Technology Assessment

Technology Assessment Program

Retinal Prostheses in the Medicare Population

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Retinal Prostheses in the Medicare Population

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Centers for Medicare and Medicaid Services requested this report from the Evidence-based Practice Center (EPC) Program at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following EPC: (To be inserted in final report) Evidence-based Practice Center (Contract Number: HHSA290201500005I).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.
If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov

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This report is based on research conducted by the (name provided in final report) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA290201500005I). The findings and conclusions in this document are those of the authors who are responsible for its contents. The findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

None of the investigators has any affiliations or financial involvement related to the material presented in this report.

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Acknowledgments

To be added to final report

Key Informants

In designing the study questions, the Evidence-based Practice Center (EPC) consulted a panel of Key Informants who represent subject experts and end-users of research. Key Informant input can inform key issues related to the topic of the technical brief. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who provided input to this report follows:

Key Informants

To be added after peer review.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

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The list of Peer Reviewers will be added to the final report.

Retinal Prostheses in the Medicare Population

Structured Abstract

Objectives. To determine the safety, efficacy and evidence of halting disease progression for retinal prosthesis systems (RPSs) and the outcomes that are and could be assessed in future studies of these devices.

Data sources. We searched MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health (CINAHL), the Cochrane Library, and PubMed (unprocessed records only), and gray literature sources, including conference proceedings from specialty societies, for studies of RPS devices published from January 1, 2000, through September 17, 2015.

Review methods. We performed redundant title and abstract screening with one reviewer's selection required for full-text article retrieval. Dual independent review was performed on all full-text articles with disagreements resolved by consensus. Data extraction was performed by a single reviewer and was fully verified by a second reviewer. Extracted data included study design, psychometric properties assessment methods based on the COSMIN checklist, patient blinding to experimental condition, outcome assessor blinding to experimental condition, experimental condition randomly presented, number of outcome assessors, country/site, number of patients enrolled, patient inclusion criteria, patient exclusion criteria, RPS treatment details, prior treatment, concurrent treatment, study duration, diagnosis, age at diagnosis, age at implantation, eye implanted, time from implantation to study participation, sex, race, visual acuity at time of implantation, outcomes, and outcome definitions.

Results. Ten studies of RPS effectiveness were included. Although some patients clearly benefit from an RPS, the evidence was insufficient to estimate the proportion of patients who would benefit. Intraoperative adverse events were typically mild but some serious adverse events were reported, including intraocular pressure increase, hypotony, and presumed endophthalmitis. One study pointed to the possibility that RPSs may provide neuroprotection. Of the 73 outcomes reported in the 10 included studies, only 4 (Early Treatment of Diabetic Retinopathy Study test, Grating Acuity Test, Chow Color Test, and Functional Low-Vision Observer Rated Assessment) had evidence of validity and/or reliability. Measures with evidence of validity and reliability that could be used in future RPS studies include full-field flash test, Grating Contrast Sensitivity, FAST instrument (Functional Assessment of Self-Reliance on Tasks), Very Low Vision Instrumental Activities of Daily Living, Modified NEI-VFQ-25 plus supplement, and the Modified Impact of Vision Impairment

Conclusions. Future studies of retinal prostheses devices should make an effort to report valid and reliable measures of day-to-day function and quality of life.

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Background

Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a collection of genotypically and phenotypically diverse eye disorders, all of which attack the rods and cones within the retina or their adjacent support cells. This inherited disease is often identified by its main clinical features, which typically include symptoms of poor night vision, visual field loss, and peripheral flickering lights. As the disease progresses and more photoreceptors are lost, patients experience an indolent, progressive constriction of their visual field until legal and functional blindness occurs, typically by age 40.[1] Upon ophthalmic examination, a triad of clinical findings is typically noted: attenuation of retinal blood vessels, "bone spicule" clumping and mottling of the retinal pigment epithelium (a single layer of pigmented cells that nourishes the retina photoreceptors), and optic nerve head pallor. All of these findings are a direct result of the main pathophysiologic action of RP, atrophy of the photoreceptor layer.

Age-related Macular Degeneration

The RP population, particularly those with vision poor enough to qualify for a retinal prosthesis system (RPS), is rather small. The broader goal for most of the companies developing retinal prostheses would be for implementation in more common disease states. The most logical of these is late-stage nonexudative age-related macular degeneration (AMD), because many of the pathologic aspects of RP for RPS can also be found in AMD, namely physiologic damage limited to the outer retina. AMD is the leading cause of irreversible visual loss in industrialized countries.[2] In the United States, it accounts for about half of severe sight loss. Although the etiology is incompletely understood, nonexudative AMD develops as a result of deposition of cellular debris—including lipids, amyloid, complement factors, and other components—in Bruch's membrane.[3,4]

Retinal Prosthesis Systems

Multiple types of ocular prosthetic devices are under development.[5-9] The devices have focused on stimulating different parts of the visual pathway, including the visual cortex,[7] the optic nerve,[8] and the suprachoroidal,[9] epiretinal,[6] and subretinal[5] spaces. Of the seven RPS devices for which there was at least one published article describing a study in humans, the only one to date to receive U.S. Food and Drug Administration (FDA) approval is the Argus II epiretinal RPS (Second Sight Medical Products, Inc., Sylmar, CA). Another device originating in the United States is the subretinal Artificial Silicon Retina (ASR), developed by Optobionics (Glen Ellyn, IL). The subretinal Alpha-IMS was created by Retina Implant AG (Reutlingen, Germany). Another German manufacturer is Fraunhofer IMS Biohybrid Systems (Duisburg, Germany), which developed the epiretinal EPIRET3 device. The IRIS device began development in Germany but is now produced by the French manufacturer Pixium Vision (Paris, France). The suprachoroidal Bionic Eye RPS comes from BionicVision in Parkville, Victoria, Australia.

Nidek Co., Ltd. (Gamagori, Japan), produces the Suprachoroidal Transretinal Stimulation (STS) Artificial Vision System.

We also identified three additional devices subjected to preclinical tests. The Boston Retinal Implant Prosthesis (Visus Technology, Inc., Boston, MA) uses a subretinal array of 16 electrodes that receives energy and data from an eyeglass-mounted video camera and radiofrequency coil, with assistance from a controller that performs image signal processing.[10] Another American device, the Photovoltaic Retinal Prosthesis (Stanford University Palanker Laboratory) has a subretinal array of thousands of photodiodes that convert light pulses to bi-phasic pulses of electric current.[11] From Japan, the Okayama University-Type Retinal Prosthesis uses a unique approach with photoelectric dye molecules coupled to polyethylene film.[12]

Alternative Treatments for Retinitis Pigmentosa and Age-Related Macular Degeneration

For RP, the current state of care is generally supportive in nature, focusing on maximizing the visual acuity of a patient (i.e., performing cataract surgery) and offering training with low-vision aids and services helping patients to function within their limited visual capacity. The absence of FDA-approved medications is not for lack of effort, with most of the past focus being on nutritional supplements. Supportive care is offered to patients with nonexudative AMD, who are also advised to quit smoking if they do. Those with intermediate or advanced disease may be advised to take antioxidant vitamins and minerals to reduce the risk of progression. For exudative AMD, the main treatment is vascular endothelial growth factor (VEGF) inhibitor therapy.

Scope and Key Questions

The scope of this review is defined below according to the PICOTS framework (population, intervention, comparators, outcomes, timing, and setting; see Table A). Key questions (KQs) appear below. Figure A presents an analytic framework that depicts KQs, populations, treatments, patient-centered outcome measures, and associated psychometric properties.

Table A. PICOTS framework

PICOTS component	Description
Patients	Individuals in the Medicare population with low vision and retinal degenerative disorders or macular disorders
Intervention	Retinal prosthesis system devices
Comparators	Best supportive care (both retinal degenerative disorders and macular disorders); pharmacologic therapy, photodynamic therapy, laser therapy (macular disorders)
Outcomes	Health-related quality of life, activities of daily living, instrumental activities of daily living, visual function, visual acuity, changes in concurrent treatments/supportive care
Timing	Any
Setting	Any

KQ1A: What outcome measures have been used in studies of RPSs?

KQ1B: What are the psychometric properties of the health-related quality of life (HRQoL), ability to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs), visual function, and other measures used in the studies?

KQ1C: What other reliable and valid measures could be used in future studies of RPSs to demonstrate improvement in HRQoL, ability to perform ADLs and IADLs, visual function, and other functions?

KQ2: What is the evidence that HRQoL, ability to perform ADLs and IADLs, visual function, and other outcomes are improved in patients who use an RPS compared with baseline (or device off or untreated eye) and compared with alternative treatments?

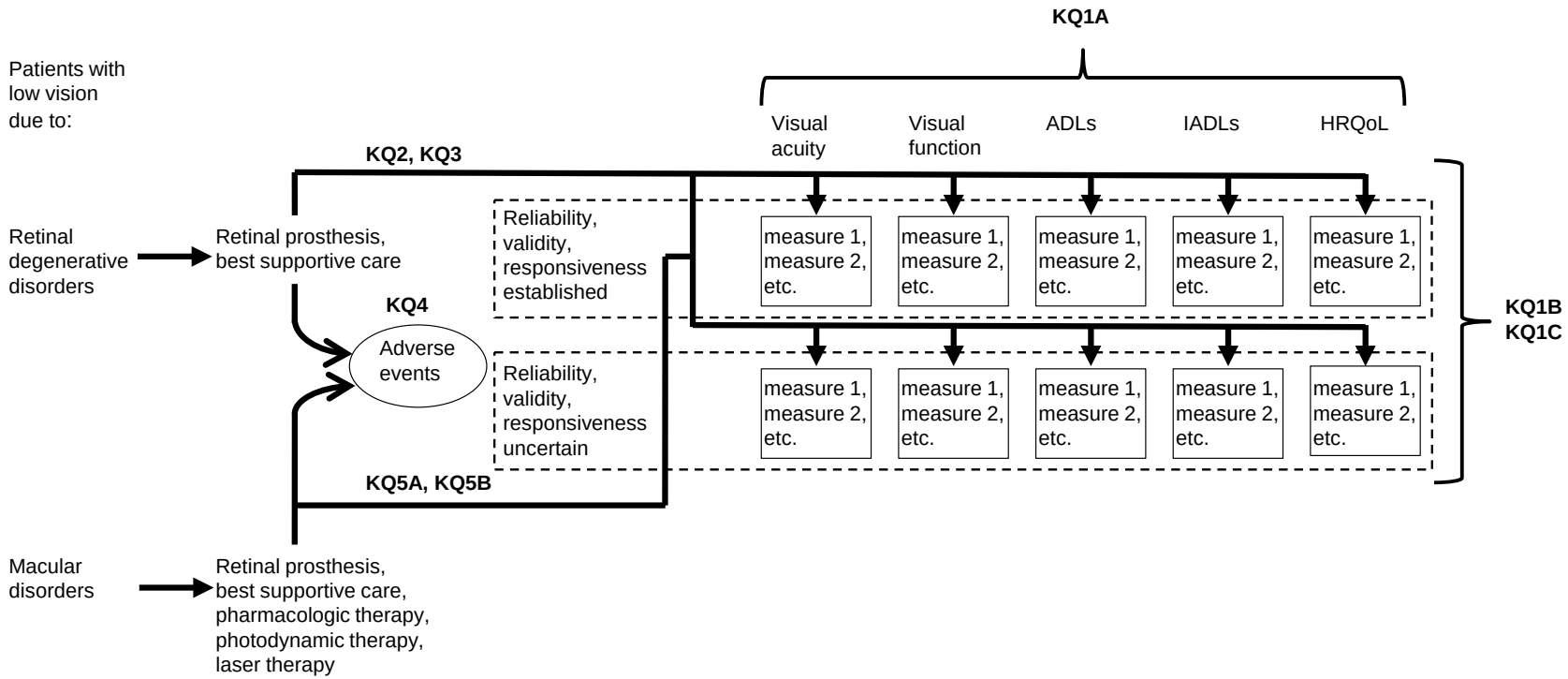
KQ3: What is the evidence that the use of RPS arrests the progression of RP?

KQ4: What is the evidence on adverse events associated with the use of RPS?

KQ5A: What is the evidence on off-label use of RPS?

KQ5B: From a narrative review of the literature, are other uses suggested for RPS?

Figure A. Analytic Framework



Note: Examples of outcome measures for which psychometric properties have been established or are uncertain could include visual acuity measures such as the Basic Grating Acuity Test and the Freiburg Acuity and Contrast Test. Examples of visual function measures may include the Basic Assessment of Liight and Motion and the Functional Low-vision Observer Rated Assessment.

Abbreviations: ADLs = activities of daily living; HRQoL = health-related quality of life; KQ = Key Question; IADLs = instrumental activities of daily living;

Methods

Literature Search Strategy

Medical librarians performed systematic literature searches following established systematic review protocols. In seeking references for RPS devices, we searched the following databases using controlled vocabulary and text words: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health (CINAHL), the Cochrane Library, and PubMed (unprocessed records only). The search concerning RPS devices covered the literature published from January 1, 2000, through September 17, 2015.

We included RPS device articles that met the following criteria: reported use of an RPS device in development or on the market, reported at least one patient-centered outcome, included any number of human participants with any retinal degeneration disorder or macular disorder diagnosis, described any study design, and was published in any language. We excluded studies of the IRIS system because the current version began studies only in late 2015. For psychometric properties (KQ1B and KQ1C), we required that articles be published in English; be primarily designed to evaluate reliability, validity, and/or responsiveness of relevant outcome measures; and have at least two-thirds of patients with very low vision (as defined by logarithm of the minimum angle of resolution [logMAR]≥1.0 and/or visual field ≤20 degrees). Correlations between different outcome categories (e.g., visual acuity and quality of life) were not taken as validity studies because they measure fundamentally different traits.

We performed dual independent review of abstract and full articles using the Distiller SR tool (Evidence Partners, Ottawa, Ontario, Canada). Extracted data were stored in Microsoft Word and Microsoft Excel files. Please refer to the review protocol (http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/rentinal-prosthesis-protocol.pdf) for more details about the methods.

Risk-of-Bias Assessment of Individual Studies

Because we did not identify any randomized controlled trials, risk-of-bias assessment of RPS device studies focused on single-group designs (case series: pretest-posttest, posttest only, device ON/OFF, fellow eye). We selected seven pertinent risk-of-bias items from the Agency for Healthcare Research and Quality (AHRQ) Methods Guide[13] (i.e., control for confounding, concurrent interventions, fidelity to protocol, low attrition, outcome assessor blinding, outcome definition/implementation, and prespecified outcomes). Each study was categorized as Low, Moderate, or High risk of bias. For studies addressing psychometric properties of outcomes, we based risk-of-bias assessments on the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist.[14] This instrument contains recommended items for internal consistency reliability, test-retest reliability, face validity, construct validity, and responsiveness.

Data Synthesis

Due to the designs of the studies (i.e., single-group designs), this review was limited to qualitative synthesis. To permit a clear synthesis, we placed each reported outcome into one of six categories: visual acuity, visual field, color vision, laboratory function (e.g., functioning during a test such as finding a door), day-to-day function, and quality of life.

Strength of the Body of Evidence

We used the strength-of-evidence grading approach described in the AHRQ Methods Guide.[13] Domains addressed included the following: study limitations, directness, consistency, precision, and reporting bias. If relevant, we also considered a dose-response association (e.g., whether more electrodes yielded greater effects) and magnitude of effect. We did not use the domain involving plausible confounders reducing an observed effect, because studies did not have separate control groups. Based on the domains, we assigned a grade of High, Moderate, Low, or Insufficient, according to definitions stated below.

Table B. Evidence grade definitions

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Thus, when the evidence did not permit a conclusion (that RPS either improves or does not improve an outcome), we rated the evidence as Insufficient. A lack of statistical significance was not assumed to imply the lack of an effect, since nonsignificance may simply mean low statistical power. We rated the strength of evidence only for KQ2 and the following outcomes because of their relative importance: visual acuity, visual field, laboratory function, day-to-day function, and quality of life. We did not rate the strength of evidence for other outcomes or other KQs.

Results

Results of Literature Searches

We recorded our process of reducing our initial list of 5,637 potentially relevant publications to a final included set of 34 publications. We excluded 2,430 publications at the title level (they were not relevant to the topic), and another 2,628 at the abstract level. The most common reasons for exclusion at the abstract level were wrong population (1,083 exclusions) and a lack of psychometric property data in studies being considered for KQ1B or KQ1C (858 exclusions). We examined 579 articles in full, and excluded 545 of these for various reasons, the most common being wrong or unclear population (219 exclusions) and no psychometric data (120 exclusions). A complete list of articles excluded at the full-text level appears in Appendix B. The 34 included publications described 19 unique studies.

Key Question 1A. Outcome Measures Used in RPS Studies

- For KQ1A we included 25 publications of 10 RPS studies.

- The 25 publications reported 73 different outcomes. Most outcomes involved visual acuity (59 percent) or laboratory function (27 percent). Four studies measured day-to-day visual function, and one study measured vision-specific quality of life.
- Only one outcome was reported by 3 or more of the 10 studies. It was the percentage of patients who passed the light localization task of the Basic Assessment of Light and Motion (BaLM) test. Little consensus exists among authors of RPS studies about which specific measures are important.

Key Question 1B. Psychometric Properties of Outcome Measures Used in RPS Studies

The Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale has acceptable test-retest reliability, but no included studies measured its validity or responsiveness.

- The Grating Acuity Test (GAT) and the Chow Color Test (CCT) have acceptable test-retest reliability and construct validity, but no included studies measured their responsiveness.

The Functional Low-Vision Observer Rated Assessment (FLORA) has acceptable face validity, but no included studies measured its reliability or responsiveness.

Key Question 1C. Psychometric Properties of Other Possible Outcome Measures

- For measuring vision in relative darkness, the full-field flash test has better psychometric properties than either dark adaptometry or dark-adapted Humphrey perimetry. For the latter two tests, many patients with RP do not provide sensible results.
- For measuring contrast sensitivity, the Grating Contrast Sensitivity (GCS) has better test-retest reliability than the Pelli-Robson test. The Pelli-Robson test may not produce meaningful results in some patients with RP, because of their limited vision. However, the validity of the GCS can be questioned, as it appears to overestimate patients' contract sensitivity.
- The FAST instrument (Functional Assessment of Self-Reliance on Tasks) has acceptable reliability, validity, and responsiveness. Further, its psychometric properties are better than those of the Veteran's Administration-13 (VA-13). Both clinician-completed and patient-completed versions of the FAST instrument have reliability and responsiveness, but they yield somewhat different answers.
- The Very Low Vision Instrumental Activities of Daily Living (IADL-VLV) has acceptable reliability, validity, and responsiveness.
- The Modified National Eye Institute Visual Function Questionnaire 25 item (NEI-VFQ-25) plus supplement and the Modified Impact of Vision Impairment (IVI) each has acceptable reliability and validity; no included studies measured their responsiveness.

Key Question 2. Effect of RPS on Health-related Quality of Life, Activities of Daily Living, Visual Function, and Other Outcomes

- Some patients clearly benefit from RPS, but evidence is insufficient to estimate the proportion of patients who would benefit.

- Visual acuity was improved in 20 percent to 100 percent of patients with an implanted device.
- Visual fields were improved in 17 percent to 100 percent of patients with an implanted device.
- One study assessed color vision and found one of six patients improved.
- Laboratory function measures were varied and patients improved on some tasks but not others.
- Day-to-day function measures were varied and patients improved on some tasks but not others.
- Quality of life was assessed in one study and found not to be reduced in patients who had a device implanted and explanted.

Key Question 3. RPS to Arrest the Progression of Retinitis Pigmentosa

- Limited evidence has been interpreted as possibly indicating that implanted RPS devices may stop the progression of RP. Patients implanted with the Argus II for 12 months experienced improved visual fields even when the system was in OFF mode.
- Evidence from animal studies has suggested a possible neuroprotective effect from electrical stimulation of the retina, mediated through induction of certain growth factors.
  - Electroretinographic waveforms in rat eyes with an active implant experienced temporary preservation compared with unoperated rate eyes through 6–7 weeks of followup.
  - Electroretinographic b-waves were significantly larger in rat eyes with active implants versus rat eyes without active implants at the 4- to 6-week followup.
  - Rat eyes with and without active implants had similar results for electroretinographic a-waves.
  - Rat eyes with active implants had four to six rows of photoreceptors, compared with a single sparse layer of photoreceptor cells in unoperated eyes 8 weeks after implantation.
  - Photoreceptor preservation occurred in all rat eyes that received an implant, even if it was an inactive implant.
  - Expression of fibroblast growth factor 2 (Fgf2) was significantly higher in rat eyes with active implants by postoperative day 9 compared with eyes with minimally active implants, eyes that underwent sham surgery, and unoperated eyes, and a dose-response relationship was evident.
  - Rat eyes with active implants and those without an active implant were similar on growth factor expression of fibroblast growth factor 1 (Fgf1), ciliary neurotrophic factor (Cntf), insulin-like growth factor (Igf), glial cell line–derived neurotrophic factor (Gdnf), and brain-derived neurotrophic factor (Bdnf).

Key Question 4. Adverse Events of RPS

- Intraoperative adverse events occurred in just over half of studies reporting this outcome, with injury to the optic nerve being the most serious.
- Postimplantation adverse events were common and typically mild, including inflammation, temporary intraocular pressure increase, eye scratchiness, and eye-movement restrictions.

- Intraoperative explantation adverse events were reported in half of the studies reporting this outcome, the most serious being a central retinal defect caused by removal of loose tacks.
- Post-explanation adverse events were reported by half of the studies reporting this outcome, with the most serious events including a decrease in visual acuity and a retinal detachment.
- Serious adverse events were reported by just under half of the studies reporting this outcome and included intraocular pressure increase, hypotony, and presumed endophthalmitis.
- Device-related adverse events were reported by one-third of studies reporting this outcome and included device failure and need for retacking.
- Adverse events at the long-term followup were reported by just over half of studies reporting this outcome and were varied.

Key Question 5A. Off-label Use of RPS

- One clinical trial of Argus II in patients with severe dry AMD who are legally blind is currently under way and due to be completed by June 2019.

Key Question 5B. Other Uses of RPS

- We did not identify any studies of RPS devices being used for nonvisual purposes.

Discussion

Key Findings and Strength of Evidence

The retinal prosthesis system (RPS) studies assessed in this review reported 73 different outcomes, mostly dealing with visual acuity (59 percent) or laboratory function (27 percent). Day-to-day visual function and quality of life were rarely measured. Little consensus exists among authors of RPS studies about which specific measures are important.

There is some evidence for the validity and/or reliability of the Early Treatment of Diabetic Retinopathy Study (ETDRS), Grating Acuity Test (GAT), Chow Color Test (CCT), and Functional Low-Vision Observer Rated Assessment (FLORA). No included evidence on patients with very low vision addressed the validity or reliability of other outcomes reported in the RPS studies.

Future RPS studies should consider measuring the following outcomes because some evidence shows that they are valid and/or reliable measures: full-field flash test, Grating Contrast Sensitivity (GCS), the patient and clinician version of the Functional Assessment of Self-Reliance on Tasks (FAST) instrument, the Very Low Vision Instrumental Activities of Daily Living (IADL-VLV), the Modified National Eye Institute Visual Function Questionnaire 25-item (NEI-VFQ-25) plus supplement, and the Modified Impact of Vision Impairment (IVI).

During our interviews with KIs, in particular patient/advocate KIs, we learned that patients vary in what they expect from a treatment like RPS implantation. Some patients hope to have their sight restored to "normal" vision. Other patients would be satisfied with more modest gains, such as the ability to color coordinate their clothing, use a color-contrast cutting board, or, for those patients with comorbid insulin-dependent diabetes, give themselves insulin injections. Retinal surgeons performing RPS implantation need to accurately present the full range of likely

visual acuity gains and the possibility that any individual patient may not benefit from an implant.

When choosing outcomes to include in future RPS studies, investigators should routinely measure QOL and ADLs in addition to traditional visual acuity measures, as these measures are interrelated. Small gains in any vision measure (acuity, visual field, contrast sensitivity, color vision) has the potential to bring about clinically meaningful changes in QOL and ADLs from the patient's perspective.

Although some patients clearly experienced improved visual acuity, visual field, and visual function, the percentages varied greatly among studies of Moderate to High risk of bias. Thus, evidence is insufficient to estimate the proportion of patients who will benefit from an RPS.

There is some suggestion, based on both animal and human studies, that RPSs may have a neuroprotective effect that causes at least a temporary increase in vision in areas far away from the implantation site.

Intraoperative adverse events were reported in about half of all included studies, the most serious of which included injury to the optic nerve and central retinal defect. Postimplantation adverse events were common and typically mild, including inflammation, temporary intraocular pressure increase, eye scratchiness, and eye-movement restrictions. Serious adverse events were reported by just under half of the studies reporting this outcome and included intraocular pressure increase, hypotony, and presumed endophthalmitis.

Table C. Strength of evidence for effectiveness

Strength-of-Evidence Domain	Visual Acuity	Visual Field	Laboratory Function	Day-to-Day Function	Quality of Life
Study Limitations	Moderate	Moderate	Moderate	High	Moderate
Directness	Direct	Direct	Direct	Direct	Direct
Consistency	Inconsistent	Inconsistent	Inconsistent	Inconsistent	Inconsistent
Precision	Imprecise	Imprecise	Imprecise	Imprecise	Imprecise
Reporting Bias	Undetected	Undetected	Undetected	Undetected	Undetected
Grade	**Insufficient**	**Insufficient**	**Insufficient**	**Insufficient**	**Insufficient**

Applicability

The patients enrolled in the 10 included RPS publications had RP, choroideremia, rod-cone dystrophy, or Bardet-Beidl syndrome and very low vision (counting fingers to no light perception) and are therefore representative of patients who will receive RPS devices in the future. As there are no other treatments for patients with late-stage disease, the comparators used in these studies (pre- vs. post-implantation, system ON vs. OFF) were appropriate.

The maximum duration of study followup was 7 years. In the Argus II study, 24 of 30 patients still had functioning devices at a mean of 6.2 years' followup. Because patients as young as 25 years may receive this device, longer term followup is needed. One single-patient cadaver study suggested that the Artificial Silicon Retina device had a functional life expectancy of about 20 years.

Outcomes reported in these studies were varied, making study-to-study comparisons difficult. They were often not measured with tools that have been shown to be valid and/or reliable in very-low-vision populations.

Only a limited number of sites are permitted to perform Argus II surgery, but that number will increase over time. Site personnel receive standardized training, so there is no reason to

believe that future patients at hospitals not included in the Argus II feasibility studies would have poorer outcomes than the original multisite trial.

Evidence Gaps/Future Research Recommendations

The first identified gap is the paucity of direct information about how RPSs affect quality of life. Only 1 of the 10 included RPS studies reported data on a quality-of-life instrument (the NEI-VFQ-25). Authors reported no statistically significant change in quality of life occurred during the study period of 2 years. This does not mean there was no change, because the study was too small (only 6 patients enrolled) to rule out the possibility of a difference. We recognize that the other reported outcomes (visual acuity, laboratory function, day-to-day function) may be surrogates for quality of life, on the premise that improved acuity will translate into improved quality of life. However, these outcomes are less patient-oriented than quality of life itself.

The second identified gap is the inability to estimate the proportion of patients who would improve after RPS implantation. Because studies used different devices, different comparators, and different outcomes (see previous section), there can be no single estimate of the proportion, because all of these aspects will likely affect improvement rates. Even controlling for the type of RPS, there was too much outcome heterogeneity to permit an estimate.

A third gap involved psychometric testing of outcome measures in patients with very low vision (K1A and KQ1B). The studies we found used relatively advanced methods for testing psychometric properties (i.e., Rasch-based analysis, separation of item difficulty from person ability). Several of these studies had devised new instruments specifically for people with very low vision. The 10 included RPS studies, however, generally did not use these tests (an exception was the studies of the Artificial Silicon Retina by Chow et al. and Geruschat et al.,[15-17] which also provided psychometric properties of certain tests). We encourage greater use of tested instruments in future studies of RPS. With greater consistency of outcome measures, future evidence reviews might be able to estimate the likelihood of improvement after RPS implantation.

Although this is not necessarily a gap, we note that we found no information on potential other uses or off-label use of RPS devices. There is one ongoing clinical trial examining use of the Argus II in patients with severe dry AMD.

Conclusion

Future studies of retinal prostheses devices should make an effort to report valid and reliable measures of important outcomes, especially day-to-day function and quality of life.

Executive Summary References

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Introduction

Recent advances in technology have permitted the first attempts to restore sight by combining a patient's native intrinsic visual pathway with advanced light sensing, signal processing, and stimulation components in the form of an ocular prosthesis. Because of the novelty that this technology represents and the recent approval by the U.S. Food and Drug Administration (FDA) for use of one such system in patients with retinitis pigmentosa (RP), the Agency for Healthcare Research and Quality (AHRQ) commissioned an Evidence-based Practice Center to prepare this Technology Assessment to provide an overview of retinal prosthesis systems (RPSs). This assessment summarizes the current state of RPS technology as well as the existing evidence addressing the clinical utility of RPSs and potential future directions for research in areas in which information is limited.

Background

Retinitis Pigmentosa

The retina is the light-sensitive layer of tissue within the eye and is responsible for converting light into electrical impulses. These impulses are delivered through the visual pathway and interpreted in the visual centers of the brain, leading to sight. Central to this functioning is the outermost layer of the retina, the photoreceptors, comprising rods and cones. These cells act as the "ignition switch" that starts the process of sight by initiating the visual pathway. Diseases that preferentially affect the photoreceptors (or their support cells, the retinal pigment epithelium) are ideally suited for sight restoration by RPSs because the rest of the native pathway remains intact.

RP is one such disease. It is a collection of genotypically and phenotypically diverse eye disorders, all of which attack the rods and cones within the retina or their adjacent support cells. This inherited disease is often identified by its main clinical features, which typically include symptoms of poor night vision, visual field loss, and peripheral flickering lights. As the disease progresses and more photoreceptors are lost, patients experience an indolent, progressive constriction of their visual field until legal and functional blindness occurs, typically by age 40.[1] Upon ophthalmic examination, a triad of clinical findings is typically noted: attenuation of retinal blood vessels, "bone spicule" clumping and mottling of the retinal pigment epithelium (a single layer of pigmented cells that nourishes the retina photoreceptors), and optic nerve head pallor. All of these findings are a direct result of the main pathophysiologic action of RP, atrophy of the photoreceptor layer.

RP is thought to occur in 1 of every 4,000 people and affects nearly 1 million people worldwide.[2-5] More than 100 different genes have been implicated as causing the various forms of RP, representing all possible modes of genetic inheritance—autosomal dominant, autosomal recessive, X-linked, and mitochondrial.[4] Despite the numerous genes associated with RP, only 60 percent of the cases can be associated with a known mutation.[4] Clinical and family histories are of extreme importance in the diagnosis of RP, because the time course of disease and prognosis are well correlated to the pattern of inheritance, with X-linked disease being the most severe and autosomal dominant RP having later onset and milder symptoms.[4,6]

Common to many inherited diseases, age of onset is typically early in life, with patients who have autosomal recessive inheritance first exhibiting symptoms at about age 10 and those with autosomal dominant inheritance around age 23.[7] This age of onset is in contrast to other, more

familiar vision-threatening maladies including cataracts, glaucoma, and age-related macular degeneration (AMD), all of which most commonly occur in elderly populations. Because of these population age differences, blindness from RP has much higher direct medical and societal costs than other common causes of vision loss.[8,9]

Age-related Macular Degeneration

The RP population, particularly those with vision poor enough to qualify for an RPS, is rather small. The broader goal for most of the companies developing retinal prosthesis technology would be for implementation in more common disease states. The most logical of these is late-stage nonexudative AMD, because many of the pathologic aspects of RP for RPS can also be found in AMD, namely physiologic damage limited to the outer retina. This work has already begun, with a clinical trial under way in patients with end-stage AMD and poor vision.[10] AMD is the leading cause of irreversible visual loss in industrialized countries.[11] In the United States, it accounts for about half of severe sight loss.

Risk factors for nonexudative AMD include smoking, hypertension, cardiovascular disease, low levels of systemic antioxidants, low dietary intake of omega-3 long-chain polyunsaturated fatty acids, high dietary intake of saturated fats and cholesterol, high body mass index, regular use of aspirin, and genetic factors.[11]

Diagnosis of AMD does not depend on the presence of visual symptoms[12] but can include metamorphopsia (distorted wavy vision), loss in visual acuity, blurred vision, scotoma (partially diminished area in the visual field), impaired color perception, and loss in contrast sensitivity. The American Academy of Ophthalmology (AAO) AMD guideline adopts a disease classification system developed for the Age-Related Eye Disease Study (AREDS) and described in 2013 by Ferris et al.[13] Early AMD is defined as a combination of multiple small drusen, few intermediate drusen, and mild retinal pigment epithelium (RPE) abnormalities (e.g., hyper- or hypopigmentation). Intermediate AMD can include numerous intermediate drusen, at least one large druse, or geographic atrophy (GA, defined as a sharply demarcated, usually round or oval area of atrophy of the RPE not involving the center of the fovea). Advanced AMD can involve one or more of the following features:

- GA of the RPE within the foveal center
- Choroidal neovascularization (CNV; choroidal angiogenesis extending through a defect in Bruch's membrane)
- Serous and/or hemorrhagic detachment of the neurosensory retina or RPE
- Retinal hard exudates
- Subretinal and sub-RPE fibrovascular proliferation
- Disciform scar

AMD is often separated into nonexudative/nonneovascular ("dry") and exudative/neovascular ("wet") subtypes. Dry AMD is more common, accounting for about 90 percent of cases. Advanced dry AMD is characterized by GA. Wet AMD can feature CNV or pigment epithelial detachment and progresses more rapidly than dry AMD.[11]

Retinal Prosthesis Systems

Multiple types of ocular prosthetic devices are under development.[14-17] The devices stimulate different parts of the visual pathway, including the visual cortex,[16] the optic nerve,[17] and the suprachoroidal,[18] epiretinal,[15] and subretinal[14] spaces. A literature search identified seven

RPS devices for which there was at least one published article describing human recipients of the technology. Regarding placement of intraocular electrode arrays/stimulation components, three implants are inserted on the retinal surface (epiretinal), two are placed in a subretinal space, and two are implanted suprachoroidally.

Of the seven RPS devices, the only one to date to receive FDA approval is the Argus II epiretinal RPS (Second Sight Medical Products, Inc., Sylmar, CA). Another device originating in the United States is the subretinal Artificial Silicon Retina (ASR), developed by Optobionics (Glen Ellyn, IL). The subretinal Alpha-IMS was created by Retina Implant AG (Reutlingen, Germany). Another German manufacturer is Fraunhofer IMS Biohybrid Systems (Duisburg, Germany), which developed the epiretinal Epi-Ret 3 device. The IRIS device began development in Germany but is now produced by the French manufacturer Pixium Vision (Paris, France). The suprachoroidal Bionic Eye RPS comes from BionicVision in Parkville, Victoria, Australia. Nidek Co., Ltd. (Gamagori, Japan), produces the Suprachoroidal Transretinal Stimulation (STS) Artificial Vision System.

In 2011, the Argus II retinal prosthesis system was approved for use in Europe, which was followed by FDA approval in 2013 for U.S. use in patients with RP.[15] This system has three parts, including an implantable 60-electrode stimulating microelectrode array, a pair of glasses with a video camera attached, and a video-processing unit worn typically on the belt of the user. The video camera captures surrounding visual images, which are processed by the wearable unit and transmitted wirelessly to the implanted array. The array then stimulates the inner retina with electrical impulses, which follow the "typical" visual processing pathway. The Argus II RPS is a second-generation unit, with the most notable difference from the first generation being an increase in the electrode-array size, from 16 to 60 electrodes.

The French manufacturer of the epiretinal IRIS device, Pixium Vision, uses extraocular and intraocular components similar to the Argus II, but the electrode array contains 150 electrodes.[19] This company is also developing the PRIMA device, not yet implanted in humans, that uses similar extraocular components, including video camera input, but introduces subretinal microchips in modules of up to several thousand electrodes. The Argus II and IRIS devices use induction for energy and data transmission, and the German Epi-Ret 3 uses video camera input with radiofrequency telemetric transmission from the eyeglass to a posterior chamber receiver. From the receiver, data is relayed via micro-cable to an epiretinal array containing 25 electrodes.

The German Alpha-IMS device may be distinguished from the Argus II, IRIS, and Epi-Ret 3 devices by its use of incident light projected through the recipient's native lens, as opposed to providing data to the electrode array via a video camera.[20] The subretinal microchip implant contains 1,500 pixels of photodiode-amplifier-electrode units that convert light into electrical pulses, delivered locally to overlying retinal neurons. A cable exits the sclera and orbit, leading to a periauricular subdermal coil that is coupled by transdermal magnetic induction with an external primary coil. A portable signal processor has knobs for adjusting contrast sensitivity and brightness.

The American Optobionics ASR device, like the Alpha-IMS device, uses incident light instead of video camera data as the input source for the prosthesis.[21] The self-contained ARS is a disc-shaped microchip containing about 5,000 microphotodiodes, each with its own stimulating electrode. Fully powered by light, this is the only device used in humans so far that has no external power source.

An article on the Australian Bionic Eye has described the device in prototype form. This report detailed a suprachoroidal array with 33 stimulating electrodes.[18] The prototype had a

helical lead wire extended from the implant to a periauricular percutaneous connector. A head-mounted video camera provided data input to the implant. The manufacturer's Web site states that other prototypes have used 25 and 44 electrodes. Next-generation models will use an eyeglass-mounted video camera, an external vision processing unit that will connect to the camera, and arrays with 98 and 256 electrodes.

The Japanese STS Artificial Vision System (Nidek) is a suprachoroidal device connected to periauricular components fixed to the skull.[22] An eyeglass-mounted video camera sends data to a controller, which relays it to a periauricular external coil coupled by induction with a secondary coil/decoder. A micro-cable extends to the array containing 49 electrodes.

Besides the seven devices for which our preliminary searches found published reports of human recipients, we identified three additional devices subjected to preclinical tests. The Boston Retinal Implant Prosthesis (Visus Technology, Inc., Boston, MA) uses a subretinal array of 16 electrodes that receives energy and data from an eyeglass-mounted video camera and radiofrequency coil, with assistance from a controller that performs image signal processing.[23] Another American device, the Photovoltaic Retinal Prosthesis (Stanford University Palanker Laboratory) has a subretinal array of thousands of photodiodes that convert light pulses to bi-phasic pulses of electric current.[24] The device's light source comes from an eyeglass-mounted LCD (liquid crystal display) microdisplay that receives images from a video camera. From Japan, the Okayama University-Type Retinal Prosthesis (OUReP) uses a unique approach of photoelectric dye molecules coupled to polyethylene film.[25] The dye absorbs light and converts it into electric potentials. Thus the film, implanted in a subretinal space, acts as both the image receiver from incident light and neuron stimulator, with no external power source.

Table 1. Retinal prosthesis system devices with published human studies

Device	Input Source	Signal Processor	Implant Placement	Electrode/ Stimulation Array	Power Source
Alpha-IMS (Retina Implant AG, Germany)	Light projected through recipient's native lens	Part of external power supply; 2 knobs allow recipient to adjust contrast sensitivity and brightness	Subretinal	Microchip containing 1,500 pixels of photodiode-amplifier-electrode units that convert light into electrical pulses, delivered locally to overlying retinal neurons via microelectrodes; power supplied through subretinal polyimide foil that exits the eye through choroid and sclera through equator	Cable exits the orbit, leads to subdermal coil fixed onto skull behind the ear; external power supply and controller attaches by transdermal magnetic induction at external primary coil
Argus II (Second Sight Medical Products, Inc., United States)	Eyeglass-mounted video camera	Video processing unit (computer), mounted on belt or shoulder strap, attached by cable to camera and to eyeglass-mounted radiofrequency transmitter coil	Epiretinal	Electronics case fixed to sclera, secured by encircling scleral buckle containing an antenna/ receiver; sclera-penetrating ribbon cable leads to the 60-electrode array	Part of video processing unit
Artificial Silicon Retina (Optobionics, United States)	Light projected through recipient's native lens	None	Subretinal	Microchip containing about 5,000 microscopic solar cells called microphotodiodes, each with its own stimulating electrode; self-contained, no cable	Microchip is powered by incident light
Bionic Eye (BionicVision, Australia)	Next-generation model will use eyeglass-mounted video camera	External vision processing unit will connect to camera	Supra-choroidal	33 stimulating electrodes	Prototype helical lead wire extends to percutaneous connector
EPIRET3 (Fraunhofer IMS Biohybrid Systems, Germany)	Eyeglass-mounted camera in extraocular component with RF transmitter; sends data and energy telemetrically	Digital signal processor, in extraocular eyeglass component, calculates a stimulation pattern	Epiretinal	After lens removal, intraocular receiver unit placed in posterior chamber receives energy and data, sends pulses along microcable to 25 stimulation electrodes	Part of extraocular component, energy sent with radiofrequency telemetry, no cables connecting extraocular and intraocular components

Table 1. Retinal prosthesis system devices with published human studies (continued)

Device	Input Source	Signal Processor	Implant Placement	Electrode/ Stimulation Array	Power Source
IRIS (Pixium Vision, France)	Eyeglass-mounted camera in extraocular component with induction transmitter that sends data telemetrically	Eyeglass-mounted signal processer connected to pocket computer with tunable software, sends signals to induction transmitter	Epiretinal	Electronics case fixed to sclera sends ribbon cable through sclera to 150-electrode array	Unclear
Supra-choroidal Transretinal Stimulation (STS)/Nidek Artificial Vision System (Nidek Co., Ltd., Japan)	Eyeglass-mounted video camera and processor send data to controller	Controller sends data to external coil, coupled by induction to implanted secondary coil, which sends data to implanted decoder, which generates biphasic pulses across internal micro-cable to individual electrodes	Supra-choroidal	Electrode array has 49 electrodes, associated intravitreal return electrode	Battery attached to controller

Regulatory Aspects of RPS

The Argus II (Second Sight Medical), a second-generation unit, has been through multiple completed clinical trials.[26,27] The FDA approval for the Argus II specifies that only patients with RP and the most severe loss of vision (light perception only or worse) in both eyes are eligible for device implantation. New quality-of-vision scales designed to better assess the changes and improvements in eyesight for patients with such severe vision loss are an active area of study.[28]

Second Sight Medical provides resources for implanting and operating the Argus II device. Surgeons receive instructions in screening patients for eligibility to receive the device, along with a recommended clinical followup schedule. A video surgeon manual describes the surgical procedure for implanting the device. Additionally, a previously trained Argus II surgeon must be present during the first surgical implantation at any new institution. Because of these requirements, as well as the high cost and limited patient pool outlined by FDA, only 18 sites across the United States are certified for implanting the Argus II (http://www.secondsight.com/stutus-us-launch-en.html). Second Sight Medical gives clinical centers a device fitting manual with instructions on how to use all device components and requires training and qualification of personnel involved in fitting the Argus II RPS. Device recipients receive a patient manual describing use of extraocular components. A visual rehabilitation guide is available for low vision therapists, along with hands-on training.

Alternative Treatments for Retinitis Pigmentosa and Age-Related Macular Degeneration

Retinitis Pigmentosa

No FDA-approved medications exist to reverse or slow the progression of RP. The current state of care is generally supportive in nature, focusing on maximizing the visual acuity of a

patient (i.e., performing cataract surgery) and offering training with low vision aids and services helping patients to function within their limited visual capacity.

The absence of a therapy is not for lack of effort, with most of the past focus being on nutritional supplements. Randomized clinical trials have been performed on potential treatments, including docosahexaenoic acid (DHA),[29,30] lutein,[31] vitamins A and E,[32] and various combinations of these agents.[33,34] Unfortunately, none of these studies showed a definitive benefit to patients with RP, with a possible small exception being vitamin A supplementation.[32] These findings however, are not without controversy, because the benefit of vitamin A was seen only in electrophysiological testing and not in any psychophysical visual parameters perceivable by patients, despite 4 years of treatment. This is particularly important in light of the expansive literature of the potential harmful effects of excessive vitamin A supplementation.[35-39]

Pharmacologic Therapies

In RP, pharmacologic attempts have been made at neuroprotection through neurotrophic factors, with trials ongoing, but those that have reported have yet to show any efficacy.[40,41] Although successful pharmacologic interventions have been developed for exudative AMD (e.g., intravitreal injection of a vascular endothelial growth factor [VEGF] inhibitor, such as aflibercept, bevacizumab, or ranibizumab, or photodynamic therapy with verteporfin), nonexudative AMD is still managed supportively.

Gene-based Therapies

Recent landmark clinical trials of *RPE65* gene therapy for *RPE65*-related early onset retinal dystrophy, a form of RP, successfully rescued visual function and improved full-field sensitivity and pupillary light reflex in a small group of pediatric patients.[42-45] Additionally, a more recent (2014) gene therapy trial replaced the *REP1* gene in another genetic eye disorder, choroideremia, and similarly found improved visual acuity and retinal sensitivity.[46] However, excitement for this modality has been tempered because a followup study conducted in patients with a recessive early-onset form (Leber congenital amaurosis) showed continued disease progression despite stable visual improvements over 3 years.[47]

Although gene therapy is promising, two hurdles make its application to RP difficult. The first is the large number of genes that converge into the phenotype of RP. For each of the 100 genes that have been associated with RP, a new therapy would need to be developed, and even then it might not resolve all RP cases because the currently known genes do not represent 100 percent of the RP cases.[48] Second, gene therapy appears to work best at rescuing failing tissue and does not appear be as effective once all function is lost. This would leave those who are currently blind without help and make early diagnosis and treatment imperative, a goal not always easily accomplished.

Low Vision Aids and Rehabilitation

Low vision rehabilitation is a multidisciplinary effort to maximize a patient's quality of life despite limited vision.[49] Ophthalmologists and optometrists make assessments and write prescriptions for any of a variety of low vision aids that use magnification, enhanced lighting, and/or voice recognition technologies. Opticians dispense the devices, and occupational therapists and other health care professionals provide training. Some Veterans Health Administration hospitals offer specific programs for low vision rehabilitation.

Scope and Key Questions

Scope of the Review

Key Questions

The first of two key objectives to be pursued in this report is to examine the psychometric properties (validity, reliability, and responsiveness) of outcome measures that have been reported in RPS device studies or may be used in the future. The second key objective is review of the evidence reported on the effects of RPS devices on patient-centered outcomes among patients with retinal degenerative disorders or macular disorders.

The scope of this review is defined below according to the population, intervention, comparators, outcomes, timing, and setting (PICOTS) framework (Table 2). Key questions (KQs) appear below.

Table 2. PICOTS framework

PICOTS component	Description
Patients	Individuals in the Medicare population with low vision and retinal degenerative disorders or macular disorders
Intervention	Retinal prosthesis system devices
Comparators	Best supportive care (both retinal degenerative disorders and macular disorders); pharmacologic therapy, photodynamic therapy, laser therapy (macular disorders)
Outcomes	Health-related quality of life, activities of daily living, instrumental activities of daily living, visual function, visual acuity, changes in concurrent treatments/supportive care
Timing	Any
Setting	Any

Key Question 1A: What outcome measures have been used in studies of RPSs?

Key Question 1B: What are the psychometric properties of the health-related quality of life (HRQoL), ability to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs), visual function, and other measures used in the studies?

Key Question 1C: What other reliable and valid measures could be used in future studies of RPSs to demonstrate improvement in HRQoL, ability to perform ADLs and IADLs, visual function, and other functions?

Key Question 2: What is the evidence that HRQoL, ability to perform ADLs and IADLs, visual function, and other outcomes are improved in patients who use an RPS compared with baseline (or device off or untreated eye) and compared with alternative treatments?

Key Question 3: What is the evidence that the use of an RPS arrests the progression of RP?

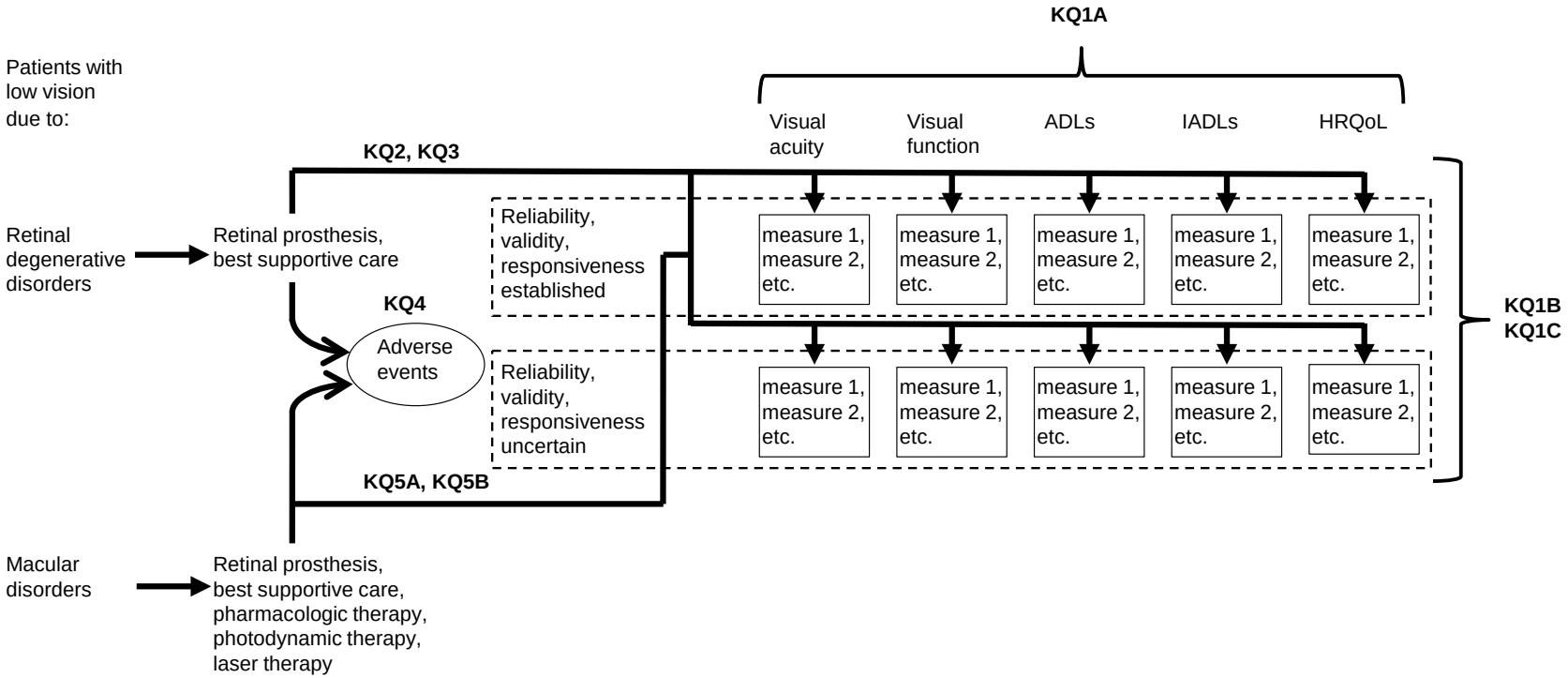
Key Question 4: What is the evidence on adverse events associated with the use of RPSs?

Key Question 5A: What is the evidence on off-label use of RPSs?

Key Question 5B: From a narrative review of the literature, are other uses suggested for RPSs?

Figure 1 presents an analytic framework that depicts KQs, populations, treatments, patient-centered outcome measures, and associated psychometric properties.

Figure 1. Analytic framework



Note: Examples of outcome measures for which psychometric properties have been established or are uncertain could include visual acuity measures such as the Basic Grating Acuity Test and the Freiburg Acuity and Contrast Test. Examples of visual function measures may include the Basic Assessment of Liight and Motion and the Functional Low-vision Observer Rated Assessment.

Abbreviations: ADLs = activities of daily living; HRQoL = health-related quality of life; KQ = Key Question; IADLs = instrumental activities of daily living;

Organization of This Report

The remainder of this report is structured as follows:

- Methods, in which we detail our processes in performing the review
- Results, in which we summarize the evidence, separately for each KQ
- Discussion, in which we highlight our key findings, provide context, discuss limitations, and summarize evidence gaps
- References
- List of abbreviations and acronyms
- Appendix A of search strategies
- Appendix B of excluded studies
- Appendix C containing all evidence tables

Methods

The methods for this systematic review follow the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm) and the PRISMA checklist. See the review protocol (http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/rentinal-prosthesis-protocol.pdf) for full details.

Topic Refinement and Review Protocol

With input from the Task Order Officer, we recruited Key Informants (KIs). As partners, the U.S. Centers for Medicare and Medicaid Services (CMS) representatives were included among our KIs. We selected additional KIs with expertise in each of the following areas: clinical and research ophthalmology, patient advocacy, health care insurance administration, psychometrics, and industry. KIs were interviewed in groups of two to four.

Each KI must have disclosed any financial conflicts of interest (COIs) greater than $10,000 and any other relevant business or professional conflicts of interest. Perspectives of KIs with potential COIs were balanced by perspectives of other neutral participants. We asked ophthalmologists about RPS candidate selection criteria—specifically about diagnoses, vision characteristics, age, and comorbidities. We also asked which management strategies for RPS devices should be compared with optimal care for RPS candidates and what comprises optimal care.

All KIs were asked which outcome measures could potentially be improved by RPS devices, in the following categories: vision, activities of daily living (ADLs), instrumental activities of daily living (IADLs), health-related quality of life (HRQoL), and others. All were asked about which outcome measures have empirically established favorable psychometric properties such as validity, reliability, and responsiveness. KIs were asked to what extent their statements were based on evidence and if so, what evidence sources they considered. At the Evidence-based Practice Center (EPC), we used KI input to refine the literature search concerning the psychometric properties of outcome measures and to enhance our understanding of the strengths and limitations of available outcome measures. The EPC followed the requirements of the Office of Management and Budget in limiting the number of KIs asked the same questions to no more than nine participants. We submitted summaries of the discussion with the KIs to the Task Order Officer.

Literature Search Strategy

Search Strategy

Published Literature Searches

Medical librarians performed systematic literature searches following established systematic review protocols. In seeking references for RPS devices, we searched the following databases using controlled vocabulary and text words: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health (CINAHL), the Cochrane Library, and PubMed (unprocessed records only). The search concerning RPS devices covered the literature published from January 1, 2000, through September 17, 2015. This time frame was chosen because preliminary searches did not

find relevant references before 2002, and early devices have either been abandoned or replaced by technologically improved versions in development or commercially available in some market. The literature search on psychometric properties of outcome measures covered the same databases as the device search but also included PsycINFO. Search limits spanned January 1, 1990, through December 14, 2015. These searches will be updated after the draft report is posted to the AHRQ website. Search strategies appear in Appendix A.

Gray Literature Search

Gray literature includes reports, articles, abstracts, and presentations produced by government agencies, private organizations, educational institutions, consulting firms, and corporations that typically do not appear in peer-reviewed journal literature. For this report, we searched gray literature sources to identify RPS manufacturers, obtain descriptions of RPS devices, and identify unpublished studies.

Among sources we consulted were conference proceedings over the past 3 years for the following organizations: the American Academy of Ophthalmology, the Association for Research in Vision and Ophthalmology, the American Society of Retina Specialists, and the Retina Society. We also searched the trial registry ClinicalTrials.gov.

Web sites and databases associated with the following institutions and organizations were searched using text words: U.S. Food and Drug Administration (FDA), CMS, U.S. Centers for Disease Control and Prevention, Healthcare Common Procedure Coding System, National Guideline Clearinghouse, the UK's National Institute for Health and Care Excellence, Trip database, Healthcare Standards database, Medline Plus, Medscape, and MediRegs. ECRI Institute resources that we searched included reports produced for ECRI's subscribers, and the periodical Health Devices. We also searched manufacturer and health care insurer Web sites. We requested that manufacturers and other stakeholders submit scientific information packets and other relevant information to the AHRQ Scientific Resource Center.

Literature searches will be updated after the draft report is posted to the AHRQ Technology Assessment Web site.

Study Selection

We included RPS device articles that met the following criteria: it reported use of an RPS device in development or on the market, reported at least one patient-centered outcome, included any number of human participants with any retinal degeneration disorder or macular disorder diagnosis, described any study design, and was published in any language. We excluded studies of the IRIS system because the current version began studies only in late 2015. For psychometric properties (KQ1B and KQ1C), we required that articles be published in English, be primarily designed to evaluate reliability, validity, and/or responsiveness of relevant outcome measures, and have at least two-thirds of patients with very low vision (as defined by logarithm of the minimum angle of resolution [logMAR] $\geq$1.0 and/or visual field $\leq$20 degrees). Correlations between different outcome categories (e.g., visual acuity and quality of life) were not taken as validity studies because they measure fundamentally different traits.

Data Extraction

We performed redundant title and abstract screening using the Distiller SR tool (Evidence Partners, Ottawa, Ontario, Canada). All articles that were excluded by one reviewer in title and abstract screening were submitted to duplicate review. Only one reviewer's selection was

required for full-text article retrieval. Dual independent review was performed on all full-text articles. Resolution of full-text article review disagreements was achieved by consensus. A PRISMA diagram was produced (see "Results of Literature Searches").

Data extraction was performed by a single reviewer and was fully verified by a second reviewer. Extracted data are stored in Microsoft Word and Microsoft Excel files. Information extracted included the following: study design, psychometric properties assessment methods (from COnsensus-based Standards for the selection of health Measurement INstruments [COSMIN] checklist items),[50] patient blinding to experimental condition, outcome assessor blinding to experimental condition, experimental condition randomly presented, number of outcome assessors, country/site, number of patients enrolled, patient inclusion criteria, patient exclusion criteria, RPS treatment details, prior treatment, concurrent treatment, study duration, diagnosis, age at diagnosis, age at implantation, eye implanted, time from implantation to study participation, sex, race, visual acuity at time of implantation, outcomes, and outcome definitions.

Risk-of-Bias Assessment of Individual Studies

Because we did not expect to identify randomized controlled trials, our risk-of-bias assessment of RPS device studies focused on single-group designs (case series: pretest-posttest, posttest only, device ON/OFF, fellow eye). These risk-of-bias items have been selected from the AHRQ Methods Guide[51]:

- Does the design or analysis control or account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?
- Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
- Did the study maintain fidelity to the intervention protocol?
- If attrition (overall or differential nonresponse, dropout, loss to followup, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
- Were the outcome assessors blinded to the intervention or exposure status of participants?
- Were outcomes assessed/defined using valid and reliable measures and implemented consistently across all study participants?
- Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?

Risk-of-bias assessment of studies addressing the effectiveness of RPS was based on seven predetermined items. To receive a rating of Low, studies needed to have a yes for the first five risk-of-bias items (confounder controlling, concurrent intervention controlling, intervention protocol fidelity, attrition handled appropriately, and outcome assessor blinding). For a rating of Moderate, studies needed at least three yes responses on risk-of-bias items 1 through 5 and a Not Reported or Yes on items 6 and 7 (outcomes assessed using valid and reliable measures and outcomes prespecified by investigators). All other studies were rated High risk of bias.

Risk-of-bias assessment of studies addressing outcome-measures psychometric properties was based on the COSMIN checklist.[50] This instrument was developed using rigorous methods including Delphi procedures. Items addressed the following domains: internal consistency, reliability, measurement error, content validity, structural validity, hypothesis testing, cross-cultural validity, criterion validity, and responsiveness.

Data Synthesis

Because of the designs of the studies (i.e., single group designs), this review was limited to qualitative synthesis. To permit a clear synthesis, we placed each reported outcome into one of six categories:

- Visual acuity
- Visual field
- Color vision
- Laboratory function
- Day-to-day function
- Vision-related quality of life

Strength of the Body of Evidence

We used the strength-of-evidence grading approach described in the AHRQ Methods Guide.[51] Domains addressed were study limitations, directness, consistency, precision, and reporting bias. If relevant, we also considered a dose-response association (e.g., whether more electrodes yielded greater effects) and magnitude of effect. We did not use the domain involving plausible confounders reducing an observed effect, since studies did not have separate control groups. We assigned a grade of High, Moderate, Low, or Insufficient, according to definitions stated below.

Table 3. Evidence grade definitions

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Thus, when the evidence did not permit a conclusion (e.g., RPS either improves or does not improve an outcome), we rated the evidence as Insufficient. A lack of statistical significance was not assumed to imply the lack of an effect, since nonsignificance may simply mean low statistical power. We rated the strength of evidence only for KQ2 and the following outcomes because of their relative importance: visual acuity, visual field, laboratory function, day-to-day function, and quality of life. We did not rate the strength of evidence for other outcomes or other KQs.

Applicability

Factors of interest in assessing applicability focused on the framework defined by population, intervention, comparators, outcomes, timing, and setting. More specifically, applicability was

determined mainly by patient-selection methods, patient-sample characteristics, intervention characteristics, and magnitude of effects on outcomes.

Peer Review and Public Commentary

The full draft report will be posted for public and peer review after review by the Task Order Officer and Associate Editor. Peer reviewers, chosen by methods similar to KI selection, will be invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report will be considered by the EPC in preparation of the final report. The dispositions of the peer review comments will be documented and posted on the AHRQ Technology Assessment Program Web site.

Results

Results of Literature Searches

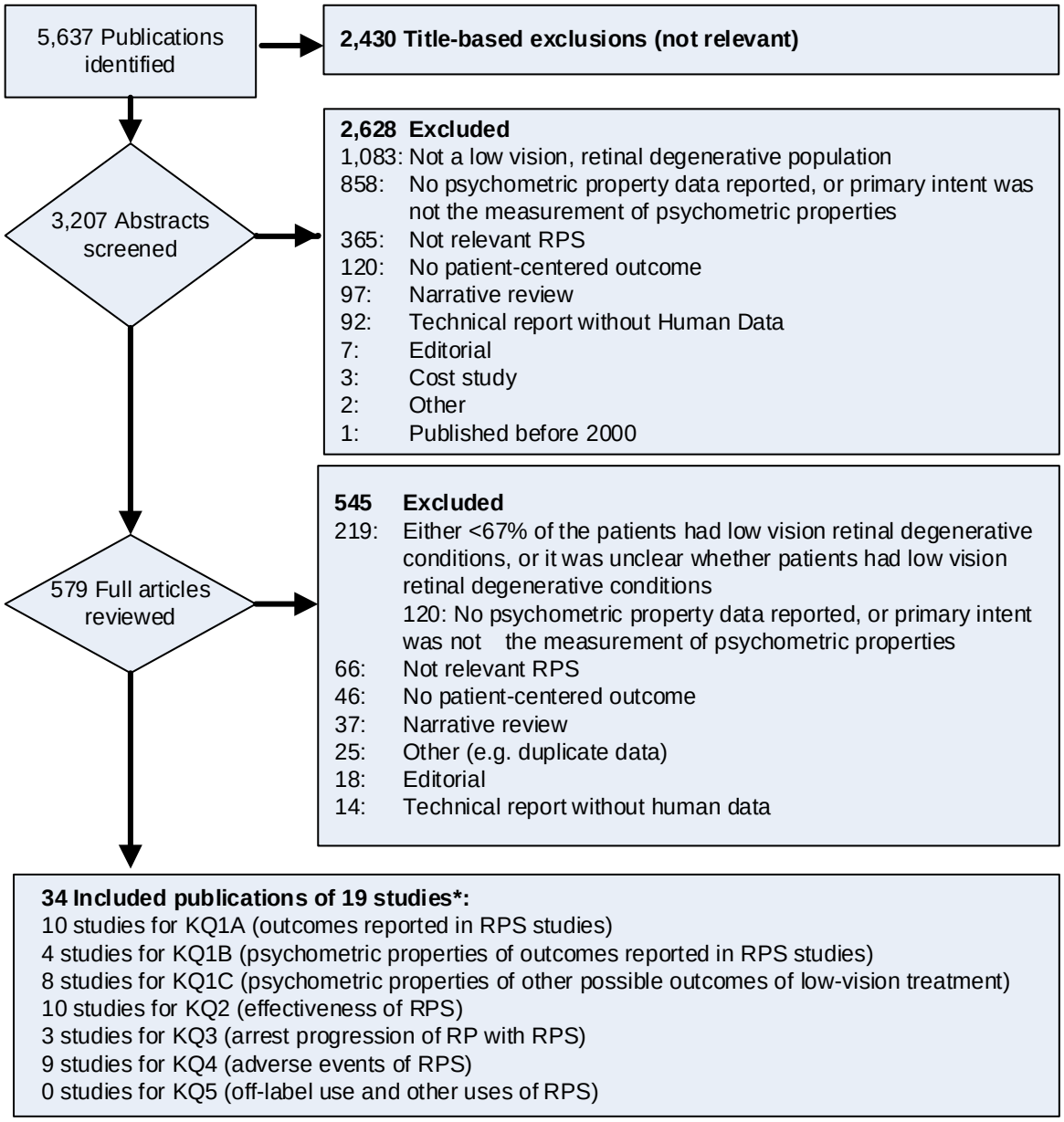
Figure 2 shows the process of reducing our initial list of 5,637 potentially relevant publications to a final included set of 34 publications. We excluded 2,430 publications at the title level (they were not relevant to the topic), and another 2,628 at the abstract level. The most common reasons for exclusion at the abstract level were wrong population (1,083 exclusions) and a lack of 2,6psychometric property data in studies being considered for Key Question (KQ) 1B or KQ1C (858 exclusions). We examined 579 articles in full, and excluded 545 of these for various reasons, the most common being wrong or unclear population (219 exclusions) and no psychometric data (120 exclusions). A complete list of articles excluded at the full-text level appears in Appendix B.

The 34 included publications described 19 unique studies. Per KQ, we included:

- Ten studies included for KQ1A (outcomes reported in retinal prosthesis system [RPS] studies)
- Four studies included for KQ1B (psychometric properties of outcomes reported in RPS studies)
- Eight studies included for KQ1C (psychometric properties of other possible outcomes of low vision treatment)
- Ten studies included for KQ2 (effectiveness of RPS)
- Two studies included for KQ3 (arrest progression of retinitis pigmentosa [RP] with RPS)
- Nine studies included for KQ4 (adverse events of RPS)
- No studies included for KQ5 (off-label use and other uses of RPS)

(These numbers do not add to 19 because some studies contributed data to multiple KQs.) The remainder of the Results section summarizes the evidence separately for each of the KQs.

Figure 2. Study attrition diagram



* The numbers do not add to 19 because some studies contributed to multiple KQs

Key Question 1A. Outcome Measures Used in RPS Studies

Description of Included Studies

For KQ1A we included 25 publications of 10 RPS studies:

- Alpha IMS study by Stingl et al., reported in 2013 and 2015[52,53]
- Alpha IMS study by Zrenner et al. 2011[14]
- Argus II study by Ho et al. 2015, also reported by other authors[15,27,54-60]
- Argus II study by Rizzo et al. 2014[61]
- Argus II study by Arevalo et al. 2015[62,63]
- Artificial Silicon Retina (ASR) study by Chow et al. 2004[21]
- Artificial Silicon Retina (ASR) extension study by Chow et al. 2010, also reported by Geruschat et al. 2012[64,65]
- Bionic Vision study by Ayton et al. 2014[18]
- EPIRET3 study by Klauke et al. 2011 and also reported by other authors[66-70]
- Suprachoroidal Transretinal Stimulation (STS) study by Fujikado et al. 2011[22]

Both Alpha IMS studies were conducted in Germany; the three Argus II studies were conducted in the United States, Europe, and Saudi Arabia; the two ASR studies were conducted in the United States; the Bionic Vision study was conducted in Australia; the EPIRET3 study was conducted in Germany; and the STS study was conducted in Japan.

The studies were all small, with enrollments ranging from 2 to 30 patients (the median was 6 patients per study). Study durations ranged from 7 weeks to 7 years. Mean patient age at implantation ranged from 40.7 to 69.5 years, and more than half of the patients were male (median 67 percent among the 9 studies reporting the sex distribution). For more information, including other patient characteristics, intervention details, comparators, and outcome data, see tables in Appendix C. This KQ focuses on types of outcome metrics used in these 10 studies.

Key Points

- The 25 publications reported 73 different outcomes. Most outcomes involved visual acuity (59 percent) or laboratory function (27 percent). Four studies measured day-to-day visual function, and one study measured vision-specific quality of life.
- Only one outcome was reported by three or more studies; it was the percentage of patients who passed the light localization task of the Basic Assessment of Light and Motion (BaLM). Seven other visual acuity outcomes were reported by two studies each. Little consensus exists among authors of RPS studies about which specific measures are important.

Detailed Synthesis

Table 4 below shows the 73 types of outcomes reported by the 10 studies. We categorized outcomes as follows:

- Visual acuity: 43 outcomes, with all 10 studies reporting at least 1 outcome
- Visual field: 4 outcomes, with 2 studies reporting at least 1 outcome
- Color vision: 1 outcome reported by a single study

- Laboratory function: 20 outcomes, with 6 studies reporting at least 1 outcome
- Day-to-day function: 4 outcomes, with 4 studies reporting at least 1 outcome
- Quality of life: 1 outcome reported by a single study

Only 1 outcome was reported by 3 or more of the 10 studies: the percentage of patients who passed the light localization task of BaLM. Seven other visual acuity outcomes were reported by two studies each: (1) BaLM, light perception subtask, percentage passing the test; (2) BaLM, movement subtask, percentage passing the test; (3) Clock task, percentage passing the test; (4) Gray levels test: percentage passing the test; (5) Direction of motion test, percentage who performed better with the device ON than OFF; (6) Grating Acuity Test (GAT), percentage whose system ON results were better than system OFF; and (7) Square localization, percentage whose system ON results were significantly better than system OFF. Thus, there is little consensus among authors of RPS studies about which specific measures are important.

Table 4. Outcomes reported in included retinal prosthesis system studies

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015[52,53]	Alpha IMS study by Zrenner et al. 2011[14]	Argus II study by Ho et al. 2015 and other authors[15,27,54-60]	Argus II study by Rizzo et al. 2014[61]	Argus II study by Arevalo et al. 2015[62,63]	Artificial Silicon Retina (ASR) study by Chow et al. 2004[21]	Artificial Silicon Retina (ASR) extension study by Chow 2010 and Geruschat 2012[64,65]	Bionic Vision study by Ayton et al. 2014[18]	EPIRET3 study by Klauke et al. 2011 and other authors[66-70]	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011[22]
Visual acuity	Ability to differentiate spatiotemporal patterns									✓	
Visual acuity	Ability to perceive 2 distinct phosphenes better than chance when stimuli were delivered through 2 channels										✓
Visual acuity	Ability to perceive phosphenes at all										✓
Visual acuity	Ability to see any light	✓									
Visual acuity	BaLM, light localization, % passing the test	✓	✓						✓		
Visual acuity	BaLM, light perception, % passing the test	✓	✓								
Visual acuity	BaLM, movement,% passing the test	✓	✓								
Visual acuity	Direction of motion test, number of correct responses				✓						
Visual acuity	Direction of motion test, % of subjects whose system ON results were better than system OFF			✓		✓					
Visual acuity	ETDRS, logMAR average							✓			
Visual acuity	ETDRS, logMAR, % who improved							✓			

Table 4. Outcomes reported in included RPS studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015[52,53]	Alpha IMS study by Zrenner et al. 2011[14]	Argus II study by Ho et al. 2015 and other authors[15,27,54-60]	Argus II study by Rizzo et al. 2014[61]	Argus II study by Arevalo et al. 2015[62,63]	Artificial Silicon Retina (ASR) study by Chow et al. 2004[21]	Artificial Silicon Retina (ASR) extension study by Chow 2010 and Geruschat 2012[64,65]	Bionic Vision study by Ayton et al. 2014[18]	EPIRET3 study by Klauke et al. 2011 and other authors[66-70]	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011[22]
Visual acuity	ETDRS: number of letters seen by each eye						✓				
Visual acuity	False-positive responses to simulation									✓	
Visual acuity	GAT, logMAR, average							✓			
Visual acuity	GAT, logMAR. % who improved							✓			
Visual acuity	GAT, % of subjects whose system ON results were better than system OFF	✓				✓					
Visual acuity	Grating visual acuity: % of subjects who scored between 2.9 and 1.6 logMAR with the system ON			✓							
Visual acuity	Grating, % who could correctly identify gratings				✓						
Visual acuity	Grid detection, % passing the test		✓								
Visual acuity	Landolt C rings, LogMAR								✓		
Visual acuity	Landolt C rings, % passing the test	✓	✓								
Visual acuity	Letter recognition, mean seconds for correctly identified letters			✓							
Visual acuity	Letter recognition, % correct			✓							

Table 4. Outcomes reported in included RPS studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015[52,53]	Alpha IMS study by Zrenner et al. 2011[14]	Argus II study by Ho et al. 2015 and other authors[15,27,54-60]	Argus II study by Rizzo et al. 2014[61]	Argus II study by Arevalo et al. 2015[62,63]	Artificial Silicon Retina (ASR) study by Chow et al. 2004[21]	Artificial Silicon Retina (ASR) extension study by Chow 2010 and Geruschat 2012[64,65]	Bionic Vision study by Ayton et al. 2014[18]	EPIRET3 study by Klauke et al. 2011 and other authors[66-70]	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011[22]
Visual acuity	Letter size reduction test, total number of letters identified correctly			✓							
Visual acuity	Motion direction test, better than chance										✓
Visual acuity	Multiple letters, % passing the test		✓								
Visual acuity	Object detection with head scanning better than chance										✓
Visual acuity	Object discrimination with head scanning better than chance										✓
Visual acuity	Pattern U in 4 directions, % passing the test		✓								
Visual acuity	Positive response to first stimulation pulses									✓	
Visual acuity	Reading letters, % passing the test	✓									
Visual acuity	Reliable phosphene precepts								✓		
Visual acuity	Seeing optotypes at all								✓		
Visual acuity	Seeing visual percepts at all									✓	
Visual acuity	Seeing visual percepts in all sessions									✓	
Visual acuity	Single letter detection, % passing the test		✓								

Table 4. Outcomes reported in included RPS studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015[52,53]	Alpha IMS study by Zrenner et al. 2011[14]	Argus II study by Ho et al. 2015 and other authors[15,27,54-60]	Argus II study by Rizzo et al. 2014[61]	Argus II study by Arevalo et al. 2015[62,63]	Artificial Silicon Retina (ASR) study by Chow et al. 2004[21]	Artificial Silicon Retina (ASR) extension study by Chow 2010 and Geruschat 2012[64,65]	Bionic Vision study by Ayton et al. 2014[18]	EPIRET3 study by Klauke et al. 2011 and other authors[66-70]	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011[22]
Visual acuity	Single pulse oblique line, % passing the test		✓								
Visual acuity	Single pulse, row of 4 electrodes, % passing the test		✓								
Visual acuity	Square localization, mean distance from target center				✓						
Visual acuity	Square localization: % of subjects whose system ON results were significantly better than system OFF			✓		✓					
Visual acuity	Word recognition, number of 4-letter words identified			✓							
Visual acuity	Word recognition, number of 3-letter words identified			✓							
Visual acuity	Word recognition, number of 2-letter words identified			✓							
Visual field	Central Humphrey visual field test, % who consistently positively responded						✓				
Visual field	Goldmann visual field test, % who improved				✓						
Visual field	Subjective visual field, % of patients who indicated perception of light sensation to infrared light in the projected visual field						✓				

Table 4. Outcomes reported in included RPS studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015[52,53]	Alpha IMS study by Zrenner et al. 2011[14]	Argus II study by Ho et al. 2015 and other authors[15,27,54-60]	Argus II study by Rizzo et al. 2014[61]	Argus II study by Arevalo et al. 2015[62,63]	Artificial Silicon Retina (ASR) study by Chow et al. 2004[21]	Artificial Silicon Retina (ASR) extension study by Chow 2010 and Geruschat 2012[64,65]	Bionic Vision study by Ayton et al. 2014[18]	EPIRET3 study by Klauke et al. 2011 and other authors[66-70]	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011[22]
Visual field	Visual field light threshold testing, % of patients who improved						✓				
Color vision	Pseudoisochromatic color plate test, % who improved						✓				
Laboratory function	Clock task, % of patients passing the test	✓	✓								
Laboratory function	Controlled mobility course, % who successfully completed the course							✓			
Laboratory function	Dining objects identification, mean score out of 4 (4 being best)	✓									
Laboratory function	Dining objects localization, mean score out of 4 (4 being best)	✓									
Laboratory function	Dining objects localization, % of patients passing		✓								
Laboratory function	Dining objects number, mean score out of 4 (4 being best)	✓									
Laboratory function	Finding the door, % of patients successful			✓							
Laboratory function	Following the line, % of patients successful			✓							
Laboratory function	Geometric shape identification, mean score out of 4 (4 being best)	✓									

Table 4. Outcomes reported in included RPS studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015[52,53]	Alpha IMS study by Zrenner et al. 2011[14]	Argus II study by Ho et al. 2015 and other authors[15,27,54-60]	Argus II study by Rizzo et al. 2014[61]	Argus II study by Arevalo et al. 2015[62,63]	Artificial Silicon Retina (ASR) study by Chow et al. 2004[21]	Artificial Silicon Retina (ASR) extension study by Chow 2010 and Geruschat 2012[64,65]	Bionic Vision study by Ayton et al. 2014[18]	EPIRET3 study by Klauke et al. 2011 and other authors[66-70]	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011[22]
Laboratory function	Geometric shape identification, % of patients passing		✓								
Laboratory function	Geometric shape location, mean score out of 4 (4 being best)	✓									
Laboratory function	Geometric shapes number, mean score out of 4 (4 being best)	✓									
Laboratory function	Grasping objects, % of patients who were better than chance										✓
Laboratory function	Gray levels test: % of patients passing the test	✓	✓								
Laboratory function	Meander Maze Tracing, whether tracing errors reduced			✓							
Laboratory function	Meander Maze Tracing, whether tracing time improved			✓							
Laboratory function	Mobility test, % of patients successful				✓						
Laboratory function	Object prehension (locate, reach and grasp), % of patients successful			✓							
Laboratory function	Reading Braille, whether single-letter recognition was better than chance			✓							
Laboratory function	Touch panel test, % of patients who were better with system ON than OFF										✓

Table 4. Outcomes reported in included RPS studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015[52,53]	Alpha IMS study by Zrenner et al. 2011[14]	Argus II study by Ho et al. 2015 and other authors[15,27,54-60]	Argus II study by Rizzo et al. 2014[61]	Argus II study by Arevalo et al. 2015[62,63]	Artificial Silicon Retina (ASR) study by Chow et al. 2004[21]	Artificial Silicon Retina (ASR) extension study by Chow 2010 and Geruschat 2012[64,65]	Bionic Vision study by Ayton et al. 2014[18]	EPIRET3 study by Klauke et al. 2011 and other authors[66-70]	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011[22]
Day-to-day function	FLORA			✓							
Day-to-day function	Patients' impression of their visual experiences in home and daily life, % reporting improvement	✓									
Day-to-day function	Patients' impression of vision improvement for specific activities (e.g., watching son play basketball), % who reported improvement							✓			
Day-to-day function	Patients' impression of visual perceptions for 7 aspects of visual function (brightness, contrast, color, shape, resolution, movement, and visual field size), % who reported improvement						✓				
Quality of life	NEI-VFQ-25 visual-specific quality of life questionnaire									✓	

BaLM=Basic Assessment of Light and Motion test; ETDRS=Early Treatment of Diabetic Retinopathy Study; FLORA=Functional Low-Vision Observer Rated Assessment; GAT=Grating Acuity Test; logMAR=logarithm of the minimum angle of resolution; NEI-VFQ-25=National Eye Institute Visual Function Questionnaire 25 item

Key Question 1B. Psychometric Properties of Outcome Measures Used in RPS Studies

Description of Included Studies

We included four studies of psychometric properties of the outcome metrics used in studies of RPS. The four studies investigated four metrics: Early Treatment of Diabetic Retinopathy Study (ETDRS), the Chow GAT, the Chow Color test (CCT), and the Functional Low-Vision Observer Rated Assessment (FLORA). For general information about the studies, patient characteristics, interventions, comparators, and outcome data, see tables in Table C-4 Appendix C.

Key Points

- The ETDRS has acceptable test-retest reliability, but no included studies measured its validity or responsiveness.
- The GAT and the CCT have acceptable test-retest reliability and construct validity, but no included studies measured their responsiveness.
- The FLORA has acceptable face validity, but no included studies measured its reliability or responsiveness.

Description of Included Studies

- Of the 10 studies included for KQ2, 9 reported adverse events (the only exception was Chow et al. and Geruschat et al. reports on the extension study).[64,65] The reported adverse event data appear in Table C-25 of Appendix C.

Detailed Synthesis

We included evidence on the psychometric properties of four outcome measurements that have been used in RPS studies: ETDRS, FLORA, the Chow GAT, and the CCT. The psychometric properties were reported in a total of four studies.[28,64,71,72] Evidence tables in Appendix C provide the following: general information about the studies (Table C-1), patient characteristics (Table C-2), details about the measurements (Table C-3), psychometric data (Table C-4), and risk-of-bias assessments (Table C-5). Below, we discuss the outcome measurements in separate sections.

Visual Acuity: Early Treatment of Diabetic Retinopathy Study (ETDRS)

The Snellen visual acuity chart is the standard chart most people associate with an eye exam and was first created in the 19th century. Despite its wide spread use even today, the visual acuity fractions are not amenable to statistical comparisons. To address this shortcoming, the ETDRS chart was developed. With standard spacing between lines and letters and with letters of equal discrimination difficulty, the chart is considered a standard measure of visual acuity for clinical trials. Results of Snellen acuity in clinical studies are typically reported on the scale of logarithm of the minimum angle of resolution (logMAR) to attempt to correct for the lack of statistical basis between different acuity lines. Normal vision is a logMAR of 0, meaning the ability to see details as small as one minute of visual acute angle (i.e., $\log_{10}(1)=0$). Legal

blindness is defined as a patient with a logMAR of 1.0 or higher, and/or less than 20 degrees of visual field. A logMAR of 1.0 corresponds to 20/200 vision as measured by the classic Snellen chart.

We included two studies of the test-retest reliability of the ETDRS.[71,72] Bittner et al.[71] performed ETDRS under regular illumination, and we judged it at Moderate risk of bias. Kiser et al.[72] performed it under both regular and dim illumination, and we judged it at Low risk of bias. Both studies reported data in terms of the coefficient of repeatability ($CR_{.95}$). This is on the scale of logMAR, and is interpreted as how much variation can be expected from an initial value (e.g., if a patient's logMAR is 1.2 at one visit, and the test has a $CR_{.95}$ of 0.15, then one would expect with 95 percent confidence that the next visit's logMAR will be within 0.15 of the first visit, i.e., between 1.05 and 1.35).

Bittner et al.[71] reported median $CR_{.95}$ values of 0.10 for patients with RP and 0.16 for patients with other retinopathies. These values are relatively low, indicating good test-retest reliability. By contrast, Kiser et al.[72] reported somewhat higher $CR_{.95}$ values, ranging from 0.13 to 0.26 for patients with RP, 0.21 to 0.27 for patients with macular degeneration, 0.18 for those with diabetic retinopathy, and 0.20 for those with other retinopathies. These medians are all for regular illumination; under dim illumination, the investigators[72] generally found similar $CR_{.95}$ values to those under regular illumination.

Neither study reported additional psychometric properties of the ETDRS.

Visual acuity: Chow Grating Acuity Test (GAT)

The GAT was developed to be more sensitive than the ETDRS for patients with very low vision. Patients are shown a series of lines in one of four orientations: vertical, horizontal, diagonal left-right, or diagonal right-left, and asked to choose which orientation they are viewing. Results are provided on the logMAR scale for easy comparison with ETDRS results. The two studies that we included[64,71] were each at Moderate risk of bias for both test-retest reliability and construct validity.

Results for test-retest reliability were good, with $CR_{.95}$ values around 0.16 for patients with RP in both studies, and even better (0.11) for patients with other retinopathies in one of the studies.[71] Both studies tested construct validity by determining the correspondence between GAT and ETDRS, and both found strong associations (e.g., a correlation of 0.92 in Chow et al. 2010),[64] with regression slopes near 1.0. These data provide evidence that GAT has good test-retest reliability and construct validity. One caveat is that both studies found that the construct validity of GAT was restricted to patients who had RP. For patients with other retinopathies, when GAT and ETDRS were compared, authors only found a weak correspondence, as GAT appeared to overestimate patients' visual acuity.

Color Vision: Chow Color Test (CCT)

The CCT was developed to be more sensitive for patients with low vision than the standard low color vision testing, the Farnsworth PV-16. The CCT is composed of both high saturation (CHS) and low saturation discs (CLS), and the best possible score is 40. One Moderate risk-of-bias study[64] has tested its test-retest reliability as well as its construct validity (by comparing CCT results to the PV-16).

For test-retest reliability, authors reported a mean $CR_{.95}$ values of 5.8. However, this mean included all patients in the study. When results were given specifically for patients with RP, $CR_{.95}$ was slightly better at 4.8. Thus, for an average patient with RP, if his or her color vision

tested at 13 of 40 at one visit (13 was the RP average), then the next visit would be expected (with 95 percent confidence) to be between 8 and 18 of 40. The median $CR_{.95}$ value for patients with macular degeneration was even lower (3.9), and they had better color vision than patients with RP (mean 30 of 40).

Regarding construct validity, because higher scores on the CCT mean better color vision but higher scores on the PV-16 mean worse color vision, good construct validity would be indicated by a large negative correlation. The study found a strong negative correlation of r=-0.77, suggesting good construct validity. Authors felt that the PV-16 was less sensitive to differences among patients, because the PV-16 scores appeared to cluster in the middle of the range, whereas for the CCT patients, scores were more evenly dispersed across its range.

Day-to-day Function: Functional Low-vision Observer Rated Assessment (FLORA)

FLORA was developed specifically for patients with very low vision and has three components: (1) patient self-report, which includes 14 open-ended questions (e.g., "What would you like me to know about how the system has affected you?"), and any of the 14 can be skipped if the assessor so decides; (2) observation of performance in 26 activities, in which the assessor observes the patient performing common activities of daily living, and any can be skipped if the assessor so decides; and (3) the case summary, which is a narrative case report summarizing the assessor's findings.

One low risk-of-bias study[28] reported the face validity of FLORA. A team of experts in blind and low-vision rehabilitation met to draft a first assessment. During multiple rounds of revision, the team reviewed commonly accepted instruments and tailored FLORA to the challenges of this population. For the self-report questions, the assessor chose to address all 14 questions for 22 of 26 patients. For the 26 activities, assessors asked patients to perform an average of 20. Based on these methods, FLORA appears to have acceptable face validity.

The study reported no other psychometric properties of FLORA.

Key Question 1C. Psychometric Properties of Other Possible Outcome Measures

Description of Included Studies

We included eight studies of the psychometric properties of other instruments that could be used to measure the effects of RPS. These studies investigated 10 outcome measures: dark adaptometry, dark-adapted Humphrey perimetry, the full-field flash test, the Pelli-Robson contrast sensitivity test, the Grating Contrast Sensitivity (GCS) test, the Veterans Health Administration's VA-13 (formerly the Blind Rehabilitation Service Follow-up Outcomes Survey), the Functional Assessment of Self-Reliance on Tasks (FAST), the Very Low Vision Instrumental Activities of Daily Living (IADL-VLV), the Modified National Eye Institute Visual Function 25 Item (NEI-VFQ-25) plus supplement, and the Modified Impact of Vision Impairment (IVI) questionnaire. For general information about the studies, patient characteristics, interventions, comparators, and outcome data, see tables C-6 through C-10 in Appendix C.

Key Points

- For measuring vision in relative darkness, the full-field flash test has better psychometric properties than either dark adaptometry or dark-adapted Humphrey perimetry. For the latter two tests, many patients with RP do not provide sensible results.
- For measuring contrast sensitivity, the GCS has better test-retest reliability than the Pelli-Robson test. The Pelli-Robson test may not produce meaningful results in some patients with RP, due to their limited vision. However, the validity of the GCS can be questioned, because it appears to overestimate patients' contrast sensitivity.
- The FAST instrument has acceptable reliability, validity, and responsiveness. Further, its psychometric properties are better than those of the VA-13. Both clinician-completed and patient-completed versions of the FAST instrument have reliability and responsiveness, but they yield somewhat different answers.
- The IADL-VLV has acceptable reliability, validity, and responsiveness.
- The Modified NEI-VFQ-25 plus supplement and the IVI each has acceptable reliability and validity; no included studies measured their responsiveness.

Detailed Synthesis

We included evidence on the psychometric properties of 10 outcome measurements that have not been used in RPS studies. Their psychometric properties were reported in eight studies.[71-78] Evidence tables in Appendix C provide the following: general information about the studies (Table C-6), patient characteristics (Table C-7), details about the measurements (Table C-8), psychometric data (Table C-9), and risk-of-bias assessments (Table C-10). Below, we discuss the outcome measurements in separate sections.

Visual Acuity: Dark Adaptometry, Dark-adapted Humphrey Perimetry, and Full-field Flash Test

We discuss the psychometric properties of dark adaptometry, dark-adapted Humphrey perimetry, and full-field flash test together, because they were directly compared in the same study[73] and were not used in any other studies. All three tests were used in patients with very low vision as an attempt to assess their visual abilities in the dark (see test details in Table C-8 of Appendix C). The study reported test-retest reliability for all three measures and also measured construct validity as the correlation between the measures. We graded the risk of bias as Low for test-retest reliability, and Moderate for construct validity.

Two of the three tests—dark adaptometry and dark-adapted Humphrey perimetry—had the problem that only about half of the patients with RP could both complete the tests and provide sensible results. By contrast, 75 of 77 patients (97 percent) could sensibly complete the full-field flash test.[73] Below, we first discuss each test's test-retest reliability, and then we turn to inter-test correlations.

For dark adaptometry, researchers determined each person's threshold for detecting faint light (with lower decibel [dB] thresholds indicating greater sensitivity), as well as the amount of time it took to determine the person's threshold (shorter time indicates greater sensitivity). They measured test-retest reliability using the coefficient of variation (CoV), which is the standard deviation (SD) of the time required to reach the person's light perception threshold divided by the average time the person needed to reach the threshold. CoV is on a percentage scale, and

lower numbers indicate greater test-retest reliability. The various patient groups in the study averaged about 10 percent to 20 percent, which is generally good. The authors did not report results specifically for patients with RP (although, as noted above, only 16 of 33 of these patients could actually complete this test).[73]

For dark-adapted Humphrey perimetry, patients focused on a red light-emitting diode (LED) in the middle of a 4- by 4-inch square after being dark-adapted. Researchers determined each person's threshold for detecting faint light over the visual field. Data were on the dB scale, with higher dB indicating greater sensitivity. The authors measured test-retest reliability using the $CR_{.95}$ (discussed earlier), which is also expressed as dB. The authors reported $CR_{.95}$ values separately for (1) rod-based sensitivity, (2) cone-based sensitivity, and (3) rod-cone sensitivity ratios. Further, they reported $CR_{.95}$ values separately for several different groups of patients (see Table C-9 in Appendix C). The three RP groups had means ranging from about 1 dB to 18 dB; mean $CR_{.95}$ values ranged from 1 dB to 10 dB. Variability within a given patient visit was less than variability across patient visits. For this report, the most pertinent finding is that only 15 of 33 patients with RP could provide sensible results.[73]

For the full-field flash test, two flashes appeared (one at maximum attenuation, the other at a level to determine the patient's threshold for detecting faint light), and each patient's threshold was determined. Higher dB thresholds indicate greater sensitivity. Test completion was not problematic, as 75 of 77 patients provided sensible results. The authors measured test-retest reliability using the $CR_{.95}$. Mean values for the full-field flash thresholds for the four RP groups (grouped by varying levels of visual acuity) ranged from 20 to 43 dB, with $CR_{.95}$ values ranging from 6 to 12 dB. For example, a typical RP-I patient (vision 20/40 or worse but with limited visual field) had a threshold of 43 dB, and one would expect with 95 percent probability that a retest would be between 37 dB and 49 dB. This appears to be reasonably good test-retest reliability.[73]

For construct validity, the authors measured two types of associations: (1) between dark adaptometry and full-field flash tests and (2) between Humphrey perimetry and full-field flash tests. The first correlation was weak (r=0.37) and the authors theorized that the adequacy of adaptometry had device concerns ("limited response range of the SST" [scotopic sensitivity test instrument]). The second correlation was stronger (r=0.60); authors noted that macular disease (MD)-I patients were outliers, and after removing them, the correlation became stronger (r=0.80). Overall, among the three methods, the data suggest that the full-field flash test is the best for assessing dark-adapted vision in patients with very low vision.[73]

Visual Acuity: Pelli-Robson Contrast Sensitivity Test

The Pelli-Robson test is a standard contrast-sensitivity test using letter charts, and two studies[71,72] have reported its test-retest reliability in patients with very low vision. The authors reported $CR_{.95}$ and median values, and results are on the logMAR scale. The moderate risk-of-bias Bittner et al.[71] study reported a median $CR_{.95}$ value of 0.14 for patients with RP and 0.24 for patients with other retinopathies. The low risk-of-bias Kiser et al.[72] study reported poorer test-retest reliability, with median $CR_{.95}$. values ranging from 0.39 to 0.49 for various RP groups. Kiser et al.[72] also reported the test-retest reliability of the Pelli-Robson test under two alternate illumination conditions: dim and glare. For dim illumination, median $CR_{.95}$ values ranged from 0.22 to 0.50 for various RP groups, whereas for glare illumination, they were 0.25 for the best-vision RP group, 0.68 for the next-best-vision RP group, and only 0.10 for the poorest-vision patients with RP.

Visual Acuity: Grating Contrast Sensitivity (GCS) Test

Bittner et al.[71] described the GCS test as an alternative to the Pelli-Robson test. Gratings are presented in varying shades of gray, and each patient's threshold is determined. This moderate risk-of-bias study reported test-retest reliability using $CR_{.95}$ values (logMAR scale). For patients with RP, results were generally good, with median $CR_{.95}$ values of 0.13 for within-visit testing and 0.15 for between-visit testing. For patients with other retinopathies, within-visit data were similarly good, however between-visit reliability was poor (medians of 0.34 and 0.41 for the two pertinent subgroups).[71]

The authors also measured construct validity by determining the correlation between the GCS and the Pelli-Robson contrast sensitivity test. Data indicated a lack of construct validity because GCS generally overestimated patients' contrast sensitivity.[71]

Day-to-day Function: VA-13 and Functional Assessment of Self-Reliance on Tasks (FAST)

We discuss VA-13 and FAST together because the two pertinent studies on these instruments were published by the same authors from a single Veterans Health Administration (VA) hospital in Tucson, AZ,[74,75] and they were the only included studies of these instruments. All patients in both studies had undergone a low-vision rehabilitation program at the Tucson VA hospital. The first study[75] compared the clinician-completed FAST (both before and after the program) to the patient-completed VA-13 (after the program), whereas the second study[74] compared the clinician-completed FAST to a patient-completed FAST (both were administered before and after the program).

Regarding reliability, only the first study reported pertinent data (Low risk of bias), and the authors measured it in three ways: (1) separation reliability, which is how well the instrument classified respondents into different levels of the trait; (2) internal consistency reliability for persons, which is whether the items are measuring the same underlying construct of patient ability; and (3) internal consistency reliability for items, which is whether the items are measuring the same underlying construct of item difficulty. They used *a priori* thresholds for acceptable levels of these metrics. For VA-13, only the second of the three had acceptable reliability, but FAST met criteria for all three.[75]

The first study also discussed face validity of each item, based on whether the distribution of pre-treatment item difficulty (assessed using a Rasch-based analysis) was "the same order of difficulty that is observed in clinical practice at admission or in pre-test self-reports."[75] For VA-13, 11 of 13 items achieved the expected ordering, and for FAST it was achieved for all 13 items. Furthermore, the VA-13 at discharge requires patients to remember their pretreatment levels of vision functionality, and therefore has less face validity.[75]

Both studies reported data on construct validity and both were at low risk of bias. Babcock-Parziale et al. theorized that the estimated item difficulties should not change before and after vision rehabilitation because the items do not change, and they found this to be true for both the VA-13 and the clinician-completed FAST.[75] Both instruments also met their criteria for response category thresholds (whether participants could discriminate between items). McKnight and Babcock-Parziale[74] assumed that item difficulty should not change depending on whether patients or clinicians complete the FAST instrument. They found a near-linear relationship between the two types of administrations (i.e., Rasch statistical analysis generally found that if an item was relatively difficult based on clinician-completed forms, it was also relatively difficult based on patient-completed forms). However, McKnight and Babcock-Parziale[74] found

real differences based on respondent, because only 55 percent of the variance in patient scores was explained by clinician scores. They performed a multiple regression to investigate this further, and found that the timing of administration (at admission or at discharge) was the primary explanatory factor.

For responsiveness (moderate risk of bias for both studies), both versions of the FAST were acceptably responsive to changes in patient abilities after the program. The VA-13, however, was judged by Babcock-Parziale et al.[75] to be insufficiently responsive, based on their opinion that amount of improvement as measured by the VA-13 was considerably less than what is typically observed in the field.

Overall, these data suggest that for veterans with low vision in Arizona, FAST is a better instrument than VA-13, and that for the FAST, patients and clinicians give different answers.

Day-to-day Function: Very Low Vision Instrumental Activities of Daily Living (IADL-VLV)

A small study in Australia (N=40) tested the IADL-VLV instrument for its reliability and validity. Patients were observed attempting up to 53 different tasks (e.g., searching a shelf for a can of tomato soup), and they were scored on successful completion and the number of attempts needed. We rated the study's data on face validity as Low risk of bias, and its data on reliability and validity as Moderate risk of bias (because of the small enrollment).[76]

For reliability, authors measured both separation reliability (how well the instrument classified respondents into different levels of the trait) and internal consistency reliability of persons (whether the items are measuring the same underlying construct of patient ability). Both metrics met the authors' predefined criteria for acceptability.[76]

For face validity, the authors began with 296 items from existing activities of living (ADLs) tools. These were reduced to 25 general activities based on importance rankings with 62 participants with severe low vision. A panel of low vision experts then reduced the 25 activities to 11, which were comprised of 53 specific tasks.[76]

The 53 tasks were then subjected to construct validity testing based on task observance in 40 legally-blind patients. Authors tested the construct validity of the 28-item instrument in 4 ways: (1) response category thresholds (whether participants could discriminate between items); (2) a test of unidimensionality based on the residuals of the first factor in principal components analyses; (3) another test of unidimensionality based on the first contrast of residuals; and (4) whether responses were associated with non-vision related aspects of health, such as age and sex. For the first three metrics, all three acceptability thresholds were met. For targeting (whether the items adequately target the ability of respondents), authors noted that the questionnaire was "slightly suboptimal," but "still well within acceptable levels." Various analyses reduced the initial 28 items into a final list of 23 items. This final list satisfied the first two metrics for construct validity. The third was not satisfied because the analyses indicated various separate domains of tasks related to table search, recognition of symbols, clock reading, signature placement, clothes sorting, and recognition of hand gestures. For the fourth metric, authors found no associations with age and sex after controlling for both cognitive impairment and depression. Thus, patients' abilities to perform the activities are associated with both cognitive impairment and depression.[76]

Quality of Life: Modified NEI-VFQ-25 Plus Supplement

The NEI-VFQ-25 is a standard instrument for assessing visual function. Stelmack et al.[77] modified it to improve the assessment of veterans with very low vision such as legal blindness. Authors started with the 25 items from the NEI-VFQ-25 as well as 14 supplemental items. Directions were modified to add consideration of low vision devices, directions were repeated if necessary because the patients frequently forgot the instructions, the driving-related items were removed (since very few of the patients were driving), and the general vision/health questions were removed (items A1 and A2 in the supplement). The final instrument contained 34 items.

Data on construct validity (Low risk of bias) involved a Rasch analysis and an assessment of whether item difficulty and/or person ability fit statistics changed before and after the low vision rehabilitation. Neither did, indicating construct validity.

For responsiveness (Moderate risk of bias), authors found that 7 of the 34 items became statistically significantly easier after treatment (see a list of the 7 items in Table C-9 in Appendix C). Furthermore, 69 of 77 patients had a higher estimate of visual ability after treatment than before treatment. The typical degree of improvement corresponded to a four-line improvement in visual acuity. These data suggest acceptable responsiveness of the modified instrument.

Quality of Life: Modified Impact of Vision Impairment (IVI) Questionnaire

The IVI questionnaire was tested in Australia by a single moderate-quality study.[78] It differs from the IADL-VLV mentioned earlier in that the IADL-VLV asks patients to perform tasks, whereas the IVI is a self-administered questionnaire to measure patients' assessments of their general abilities and difficulties. The IVI was modified by the authors in an effort to measure the functional limitations of people with severe vision loss. It contains 28 items in two domains (activities of daily living mobility and safety [ADLMS] and emotional well-being [EWB]; higher scores indicate higher functionality). An example item is "In the PAST MONTH, how much has YOUR EYESIGHT INTERFERED with...handling money" (to which the patient answers "Not at all/A Little/Sometimes/A lot/Don't do this for other reasons").

Authors reported three types of reliability: (1) separation reliability, which is how well the instrument classified respondents into different levels of the trait; (2) internal consistency reliability for persons, which is whether the items are measuring the same underlying construct of patient ability; and (3) internal consistency reliability for items, which is whether the items are measuring the same underlying construct of item difficulty. They used *a priori* thresholds for the acceptability of these metrics, and the final version of the questionnaire met all three reliability criteria.

The face validity of their modifications of the standard IVI was established through focus-group discussions and telephone interviews with vision-impaired patients, healthy controls, and professionals. The item pool was reduced from an initial 76 items to 52, and then further reduced to 28 based on telephone interviews with 198 legally blind people.

Authors tested the construct validity of the 28-item instrument in seven ways: (1) response category thresholds, which is whether participants could discriminate between items; (2) a test of unidimensionality based on the residuals of the first factor in principal components analyses; (3) another test of unidimensionality based on the first contrast of residuals; (4) targeting, which is whether the items adequately target the ability of respondents; (5) differential item functioning, which is whether sample subgroups with similar underlying ability (e.g., of different age or sex) have similar scores on the instrument; (6) whether responses were associated with patients' eye

conditions; and (7) whether responses were associated with other aspects of health. For the first three metrics, all three acceptability thresholds were met. For targeting, authors noted that the questionnaire was "slightly suboptimal," but "still well within acceptable levels."

For differential item functioning, authors tested six demographic patient characteristics that (theoretically) should not be associated with visual function scores, and none were statistically significantly associated for either domain. Thus, the questionnaire appears to specifically measure visual function and vision-related quality of life. In the sixth test, authors found that ADLMS scores were associated with the type of eye condition: patients with RP had relatively high scores, whereas those with age-related macular degeneration (AMD) and glaucoma had relatively low scores. EWB scores, however, showed no relationship with the eye condition. For the seventh and final test of construct validity, authors found that both ADLMS and EWB subscores correlated with four other measures of health (general health, other health problems, do other health problems interfere, and anxiety/depression). As expected, higher ADLMS and EWB subscores predicted better health responses to these questions.

Overall, these data indicate good reliability and validity of the modified IVI for patients with very low vision.

Key Question 2. Effect of RPS on Health-related Quality of Life, Activities of Daily Living, Visual Function, and Other Outcomes

Description of Included Studies

We included the same 10 studies that were included for KQ 1A. See Appendix C (Table C-11 through Table C-18) for more details.

Key Points

- Some patients clearly benefit from RPS, but evidence is insufficient to estimate the proportion of patients who would benefit.
- Visual acuity was improved in 20 percent to 100 percent of patients with an implanted device.
- Visual field was improved in 17 percent to 100 percent of patients with an implanted device.
- One study assessed color vision and found improvement in one patient out of six.
- Laboratory-based function measures were varied, and patients improved on some tasks but not on others.
- Day-to-day function measures were varied, and patients improved on some tasks but not on others.
- Quality of life was assessed in one study and found not to be reduced in patients who had a device implanted and explanted.

Detailed Synthesis

Below, we discuss the effectiveness evidence in six categories: visual acuity, visual field, color vision, laboratory function, day-to-day function, and quality of life. Then we provide our

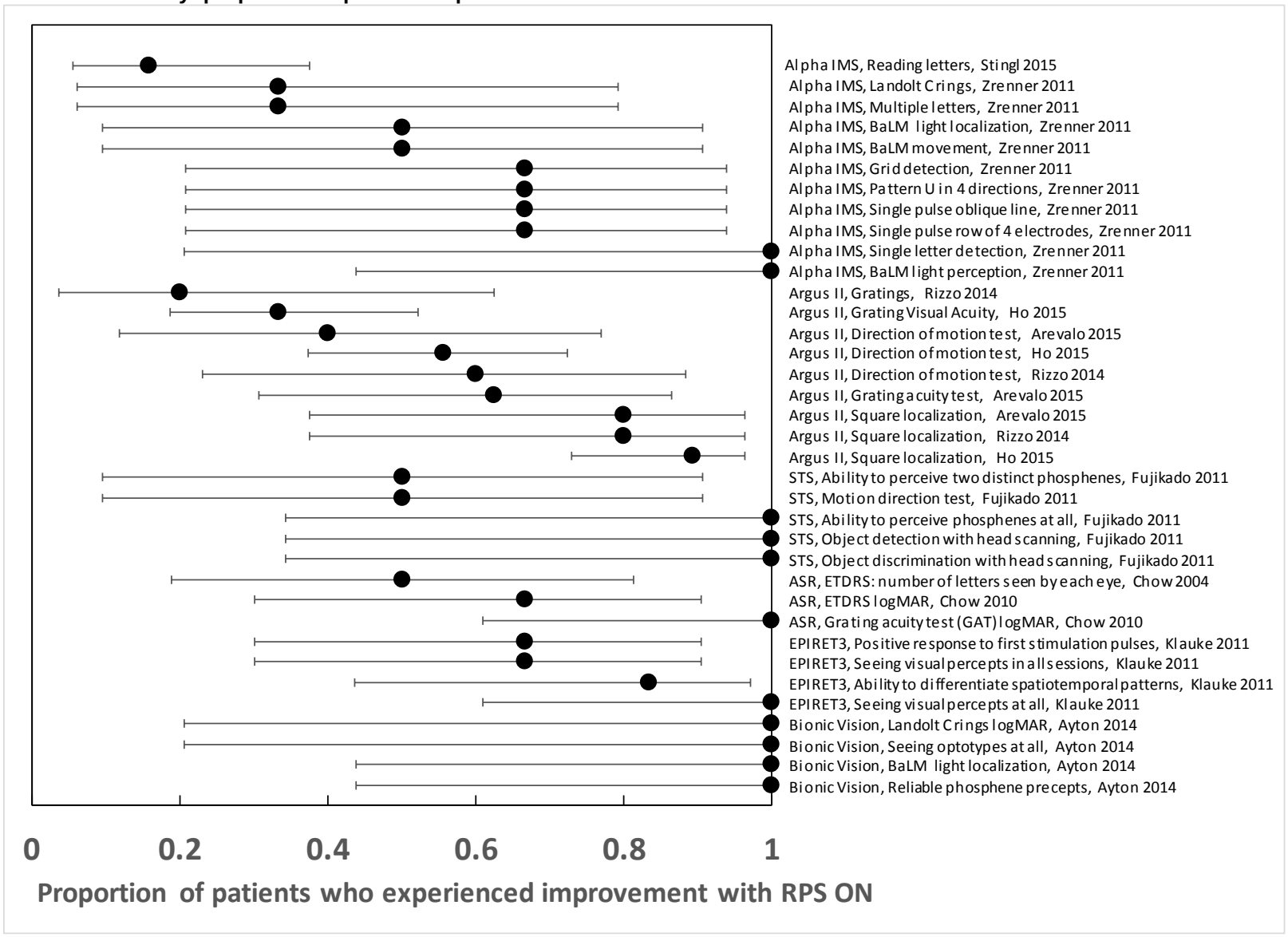
strength-of-evidence assessments for five of them (we did not assess the strength of evidence for color vision due to its lesser importance).

Visual Acuity

All 10 studies reported at least one measure of visual acuity and usually multiple measures. Although all studies found that some patients benefited from implantation with an RPS, the percentage of patients improving varied across studies. Six studies reported direction of motion.[14,15,22,27,52-63] The percentage of patients passing or with improved performance on this test ranged from a low of 21 percent in Stingl's study of the Alpha IMS to a high of 60 percent in the Rizzo study of Argus II. Four studies reported the ability to detect percepts (light).[14,18,22,66-70] In all studies, 100 percent of patients could detect percepts. Five studies reported some measure of grating visual acuity.[15,27,52-65] The percentage of patients experiencing an improvement ranged from a low of 20 percent in the Rizzo study of Argus II to a high of 100 percent in the Chow extension study of the Artificial Silicon Retina (ASR) device. Three studies, all testing Argus II, reported square localization.[15,27,54-63] The percentage of patients who performed better with the system ON versus OFF or who improved on this test ranged from a low of 80 percent in the Arevalo study to a high of 93.8 percent in the study by Ho. Three studies reported light localization.[14,18,52,53] The percentage of patients passing this test or performing better with the system in the ON versus OFF mode ranged from a low of 33 percent in Zrenner's study of the Alpha IMS device to a high of 100 percent in Ayton's study of a Suprachoroidal Retinal Prosthesis. Two studies reported Freiburg Acuity and Contrast Test (FrACT) visual acuity.[14,18] One study administered the test to one out of three patients enrolled and found that that patient did significantly better with the system ON than OFF.[18] The other study administered this test to all three patients enrolled and one out of three passed with the system in ON mode. That patient then went on to take the test with the system in OFF mode and failed.[14] Two studies, both testing the Alpha IMS device, reported light detection.[14,52,53] The percentage of patients who did better when the system was in the ON versus OFF mode ranged from 86 percent in the Stingl study to 100 percent in Zrenner's study. All other visual acuity measures were either reported by a single study or the tests performed did not seem to have been conducted in the same way across studies.

See Figure 3 for a plot of the data on the proportion of patients whose visual acuity improved when comparing ON to OFF or comparing before-implantation to after-implantation. Additional details are provided in Table C-13 in Appendix C.

Figure 3. Visual acuity: proportion of patients improved

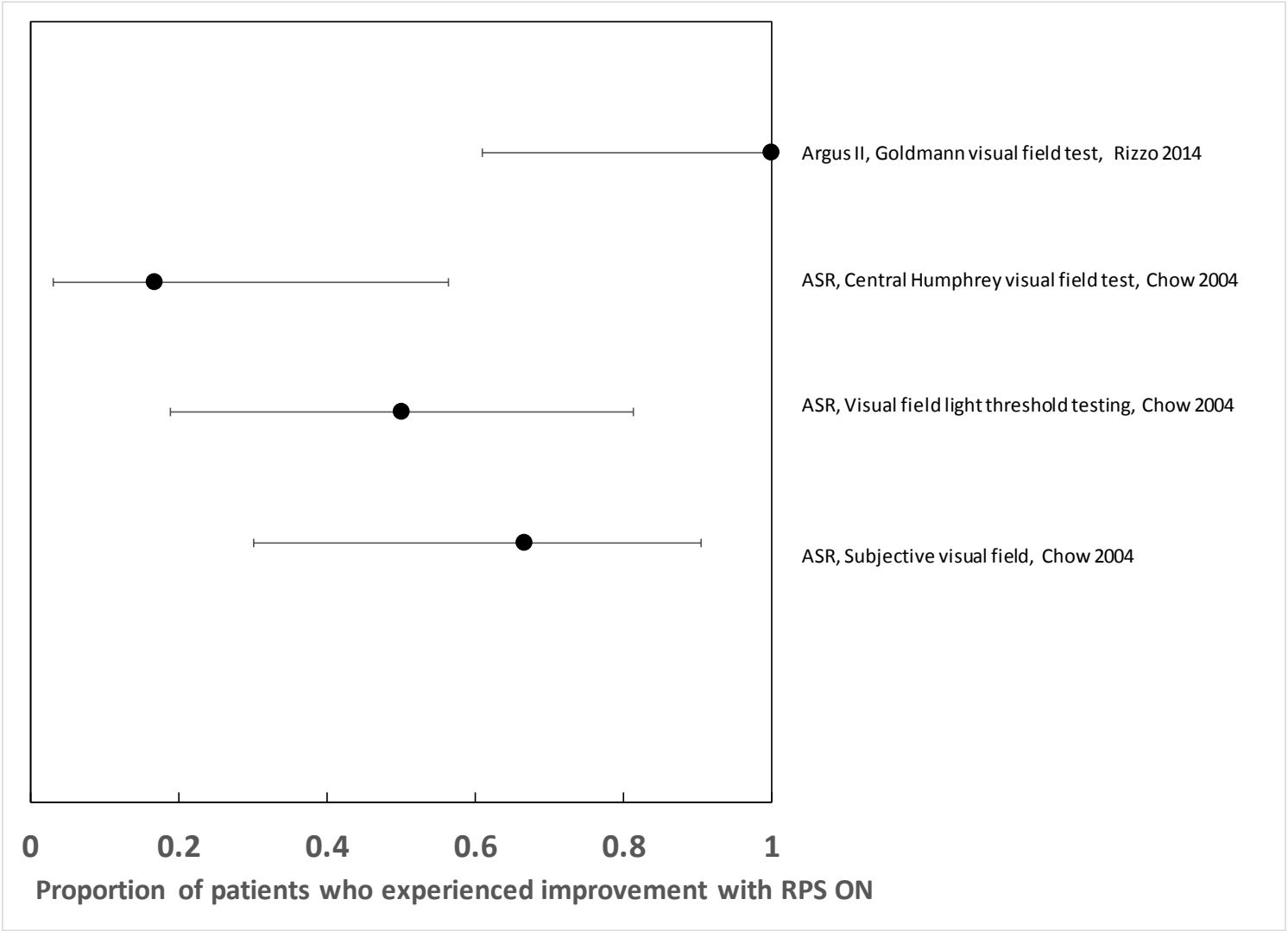


Visual Field

Two studies out of 10 reported visual field outcome data but the studies reported different measures of visual field. The Chow study of the ASR device reported Humphrey visual field test results, Nine Sector Test results, and patient subjective impression of their visual field, while the Rizzo study of Argus II reported Goldmann visual field results. Compared with the unoperated eye or their subjective impression of their visual field before implantation, patients reported their visual field improved in the following proportions: one of the six subjects tested with Humphrey visual field, three of six patients tested with the Nine Sector test, and four of six patients reporting subjective impressions of their visual field.[21] All of the patients enrolled in the Argus II study tested by Goldmann visual field improved with the system in OFF mode at the 12-month followup compared to pre-implantation.[61]

See Figure 4 for a plot of the data on the proportion of patients whose visual field testing improved when comparing ON to OFF or comparing before-implantation to after-implantation. Additional details are provided in Table C-14 in Appendix C.

Figure 4. Visual field: proportion of patients improved



Color Vision

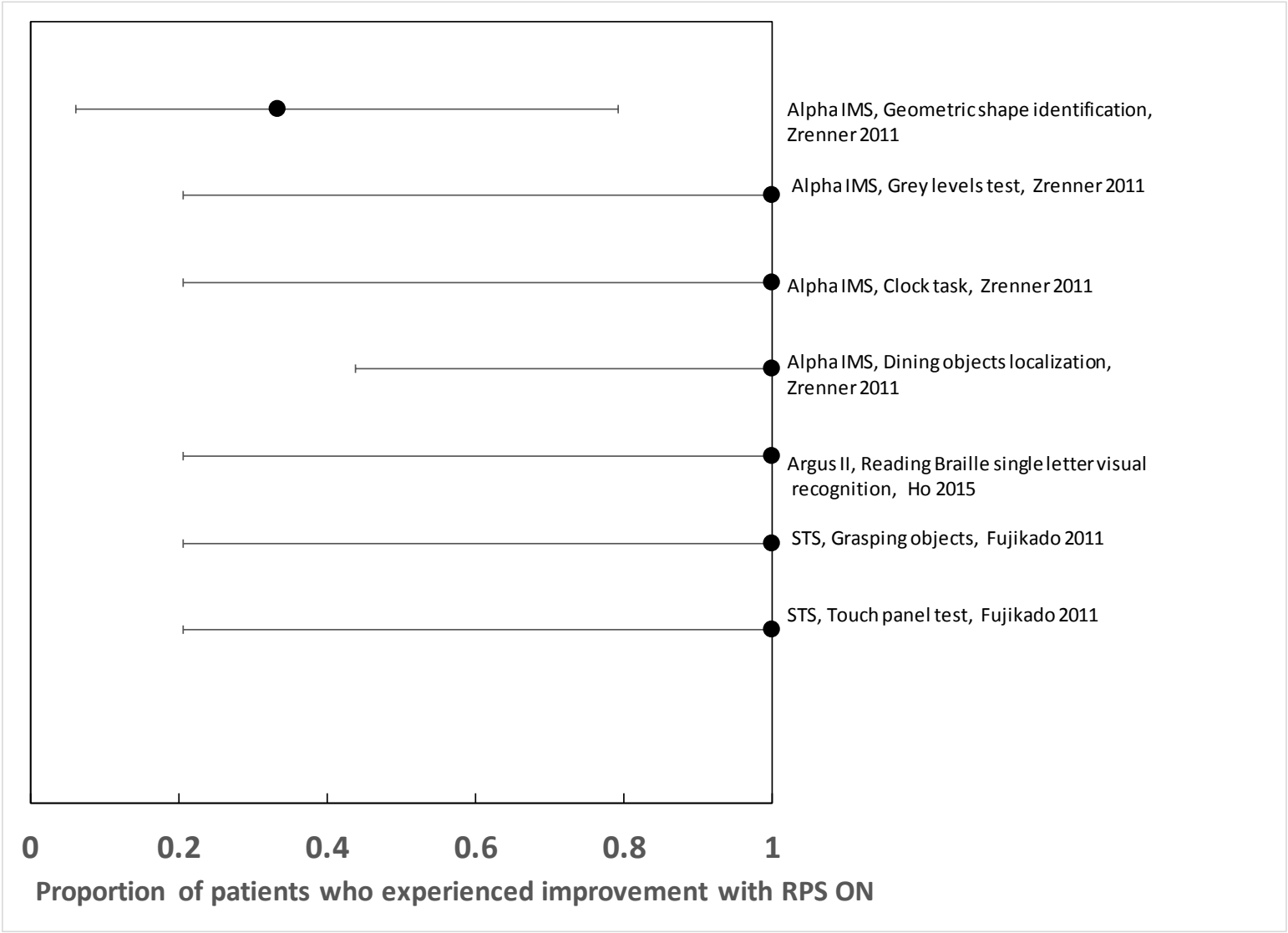
One of the 10 studies reported color vision. Chow et al. reported that one of the six patients who received the ASR implant device improved on the pseudoisochromatic test plates. The improved patient could correctly identify blue and orange dots on the control isochromatic plate and red and green dots on the test plate in the operated eye. This same patient reported that he gained the ability to detect colors in the environment (e.g., red and white of stop signs, green and white of street signs) after implantation. When the unoperated eye was tested, no patient could perceive or discriminate color.[21] Additional details are provided in Table C-15 in Appendix C.

Laboratory Function

Six of the 10 studies reported some measure of laboratory function. The ability to grasp an object was measured by two studies.[15,22,27,54-60] Only one patient in Fujikado's study of the Suprachoroidal Transretinal Stimulation (STS) device performed this test and outperformed chance with the system in ON mode but failed when the system was in OFF mode. Subjects in Ho's study of Argus II also performed significantly better when the device was in ON mode versus OFF mode. Multiple authors reporting on three studies reported patient performance on a mobility course.[15,27,54-61,64,65] Chow's extension study of the ASR device did not find a difference in patient performance of this task in the pre- versus post-implantation period. Ho's study of Argus II found patients performed this task significantly better with the device in the ON mode and Rizzo's study, also of the Argus II device, found all patients able to perform the task in the postoperative period. Two studies, both testing the Alpha IMS device, reported patients' abilities to recognize shades of gray.[14,52,53] Only one patient in Zrenner's study completed this test and that person passed with the system in ON mode but failed when it was turned to OFF. Stingl also found patients performed significantly better with the system ON than OFF. Two studies, both reporting on the Alpha IMS device, reported the ability of patients to read a clock.[14,52,53] Stingl found no significant benefit to having the device in ON versus OFF mode while the one patient tested in Zrenner's study passed when the system was ON but failed when it was turned OFF. These same two studies of Alpha IMS also reported the ability of patients to recognize geometric shapes and flatware.[14,52,53] Again, patients passed the test with the system in ON mode but failed when it was turned to OFF. They also did significantly better when the system was ON versus OFF in the Stingl study but only for the first few months, after which no statistically significant difference was noted. All other laboratory function measures were either reported by a single study or the tests performed did not seem to have been conducted in the same way across studies.

See Figure 5 for a plot of the data on the proportion of patients whose laboratory-based function improved when comparing ON to OFF or comparing before-implantation to after-implantation. See also Table C-16 in Appendix C for more detailed outcomes data.

Figure 5. Laboratory function: proportion of patients improved

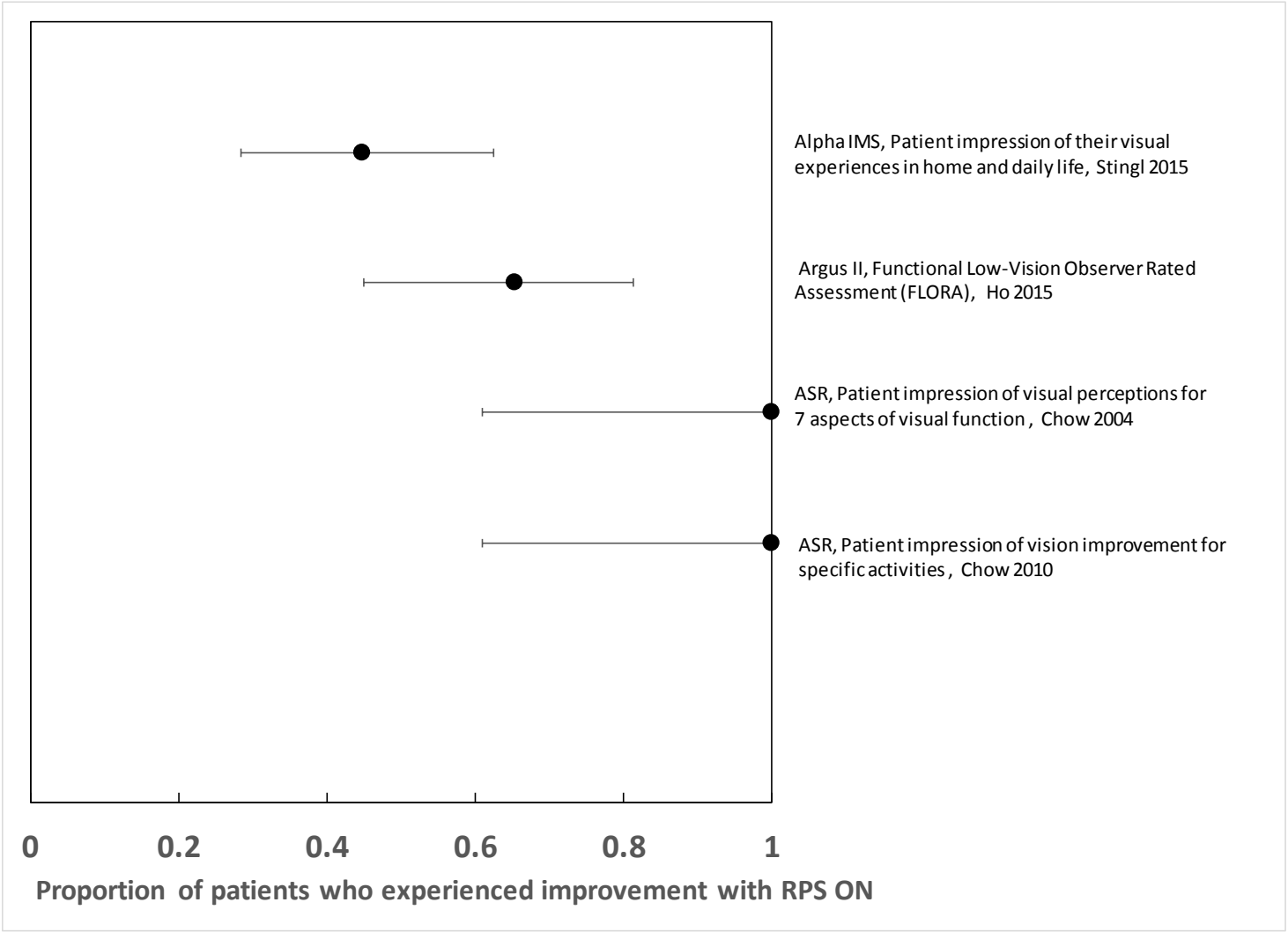


Day-to-Day Function

Four studies out of 10 reported on measures of day-to-day function. Chow asked patients to rate their subjective impression of their visual acuity by comparing their eye implanted with the ASR device to the nonimplanted eye and reported that all six patients reported better vision in the implanted eye.[21] The Chow extension study also had patients subjectively rate their visual acuity in the implanted eye but the comparator was to their memory of preimplantation visual acuity. This study also found that all six patients improved.[64,65] Stingl asked patients in whom Alpha IMS device was implanted if it was useful, a little useful, or not useful in their daily life. Of the 29 patients enrolled, 13 described the device as useful, and 8 patients each described it as a little useful or not useful.[52,53] Ho et al. and other authors reported day-to-day function with the FLORA test, which was administered at 1 year and 3 years after implantation.[15,27,54-59] Patients were asked to rate how the device impacted their daily life compared with how they remembered their functioning before implantation. At the 1-year followup, 80 percent reported their experience with the device as either positive or mildly positive, 20 percent felt neutral toward the device or they self-reported functional benefits in the past that could not be demonstrated at the time of observation, and no patients reported a negative experience. A similar pattern emerged at the 3-year followup visit, but with only 65 percent of patients rating the device's impact on their life as positive or mildly positive.

See Figure 6 for a plot of the data on the proportion of patients whose daily function improved when comparing ON to OFF or comparing before-implantation to after-implantation. See also Table C-17 in Appendix C for more detailed outcomes data.

Figure 6. Day-to-day function: proportion of patients improved



Quality of Life

One study out of 10 included data on quality of life. Klauke et al. administered the German version of the NEI-VFQ-25 to six patients who had received the EPIRET3 pre-implantation and at the 3-week, 6-month, and 27- to 29-month post-implantation visits. Patients had the device explanted after 1 month. Klauke et al. and other authors found no statistically significant difference in quality of life for patients before implantation of the EPIRET3, while the device was still implanted, or after the device had been explanted.[66-70]

Strength of Evidence

Table 5 below shows our ratings of the strength of evidence, and each domain that contributed to it.

We rated the risk of bias for all outcomes as Moderate with the exception of day-to-day function, which was rated as High. In cases where half of the studies received a study-limitation rating of Moderate and the other half a rating of High, we rated that domain as Moderate. To receive a rating of Low, studies needed to have a "yes" response for the first five risk-of-bias items (confounder controlling, concurrent intervention controlling, intervention protocol fidelity, attrition handled appropriately, and outcome assessor blinding). For a rating of Moderate, studies needed at least three "yes" responses on risk-of-bias items 1 through 5 and a "Not Reported" or "Yes" on items 6 and 7. All other studies were rated High risk of bias. See Appendix C, Table C-19 through Table C-24 for our assessment on each item for each study.

We considered all outcomes reported to be Direct because the patients enrolled in these studies had diagnoses (e.g., RP, choroideremia) and visual acuities (e.g., light perception, hand motion) that that met the U.S. Food and Drug Administration (FDA) requirements or European requirements for implantation with an RPS and because the comparators evaluated (e.g., system ON vs. OFF) are appropriate choices, given that no other treatments are currently available for this patient population.

We rated all outcomes as Inconsistent and Imprecise because although some patients clearly benefit from these devices, the percentage who benefit is highly variable across studies for any given outcome and the number of patients enrolled was small (≤30 patients).

We did not detect any evidence of reporting bias for any outcome. We made this determination by looking for studies reported at the ClinicalTrials.gov registry that should have been completed and published but for which we could not find a publication. No instances of that were found. See Appendix C, Table C-26 through Table C-33.

Overall, for all outcomes assessed, the evidence bases were found to be insufficient to estimate the proportion of patients who would benefit from RPS.

Table 5. Strength of evidence for effectiveness of retinal prosthesis systems for retinitis pigmentosa for each outcome

Strength of Evidence Domain	Visual Acuity	Visual Field	Laboratory Function	Day-to-day Function	Quality of Life
Study limitations	Moderate	Moderate	Moderate	High	Moderate
Directness	Direct	Direct	Direct	Direct	Direct
Consistency	Inconsistent	Inconsistent	Inconsistent	Inconsistent	Inconsistent
Precision	Imprecise	Imprecise	Imprecise	Imprecise	Imprecise
Reporting bias	Undetected	Undetected	Undetected	Undetected	Undetected
Strength of evidence rating	**Insufficient**	**Insufficient**	**Insufficient**	**Insufficient**	**Insufficient**

Key Question 3. RPSs to Arrest the Progression of Retinitis Pigmentosa

Description of Included Studies

Of the 10 included studies of RPS devices for KQ1A and KQ2, the two Chow studies[21,64] of the Artificial Silicon Retina (ASR) and the Rizzo study of Argus II reported the neuroprotective effects of device implantation. For details about these studies, see tables in Appendix C.

Key Points

- Limited evidence has been interpreted as possibly indicating that implanted RPS devices may arrest RP progression. Patients in whom the Argus II was implanted for 12 months experienced improved visual fields even when the system was in OFF mode.
- Evidence from animal studies has suggested a possible neuroprotective effect from electrical stimulation of the retina, mediated through induction of certain growth factors.
  - Electroretinographic waveforms in rat eyes with an active implant experienced temporary preservation compared with unoperated rat eyes through 6–7 weeks of followup.
  - Electroretinographic b-waves were significantly larger in rat eyes with active implants versus rat eyes without active implants at the 4- to 6-week followup.
  - Rat eyes with and without active implants were similar on electroretinographic a-waves.
  - Rat eyes with active implants had four to six rows of photoreceptors compared with a single sparse layer of photoreceptor cells in unoperated eyes 8 weeks after implantation.
  - Photoreceptor preservation occurred in all rat eyes that received an implant, even if it was an inactive implant.
  - Growth factor expression of fibroblast growth factor 2 (Fgf2) was significantly higher in rat eyes with active implants by postoperative day 9 compared with eyes with minimally active implants, eyes that underwent sham surgery, and unoperated eyes, and a dose-response relationship was evident.
  - Rat eyes with active implants and those without an active implant were similar on growth factor expression of fibroblast growth factor 1 (Fgf1), ciliary neurotrophic

factor (Cntf), insulin-like growth factor (Igf), glial cell line-derived neurotrophic factor (Gdnf), and brain-derived neurotrophic factor (Bdnf).

Detailed Synthesis

Of the 10 included studies of RPS devices for KQ1A and KQ2, the two Chow studies[21,64] of the ASR device and the Rizzo study of Argus II[61] reported apparent neuroprotective effects of device implantation. In Chow's extension study,[64] investigators completed two studies on Royal College of Surgeons (RCS) rats with a genetic mutation that causes photoreceptor loss starting at 12 days of age and ending by 77 days of age. They also conducted a cadaver study on one human patient with RP who had been implanted with the ASR device for 5 years before dying of natural causes.

The ASR device containing 5,000 microelectrode-tipped microphotodiodes was implanted in the superior to superior temporal retina, stimulating a small portion of the retina. Chow et al.[21] noted that visual fields distant from the implant, including the macular region and far peripheral field regions, were improved from about 1 week to 2 months after implantation, and these improvements were maintained at 6–12 months postoperatively. They theorize that patients' experiences of complex visual capabilities including improved contrast, color, resolution, movement, and visual field size are the result of low-level electrical stimulation inducing up-regulation of protective neurotrophic factors. This up-regulation, in turn, improves the functioning of remaining photoreceptors. To support this hypothesis they note that patients' improvements were not immediate after implantation but took weeks to 2 months to take effect. They also note that patients with better baseline vision, or more viable retinas, experienced greater gains from the implant than those with worse preoperative vision.[21]

In Chow's extension study,[64] RCS rats were implanted subretinally at postnatal age 3 weeks with either active or inactive ASR chips, or underwent sham surgery or no surgery. Fifteen rats were studied. Thirteen were implanted with active devices in the right eye and the left eye was either implanted with an inactive implant, had sham surgery, or had no surgery. Two of the 15 rats served as unoperated controls. Cage luminance was controlled. Implants used in this study were similar to those used in humans but modified for use in animals. Electroretinographic (ERG) recordings were performed weekly for 8 weeks after surgery, and then the animals were sacrificed.

ERG waveforms on unoperated rats demonstrated a rapid drop over the 8-week followup period while rats with an active implant experienced a temporary preservation of ERG waveforms, most notable at 4–7 weeks after implantation. At the 6-week followup, ERG amplitudes were four times greater in the rats with an active implant than in those without; however, this difference was no longer significant by the final followup visit at week 8. ERG b-wave responses were similar across groups at the 2-week followup, with the exception of the inactive implant group, whose b-waves were significantly smaller. By weeks 4 and 6, rats with the active implant had significantly larger b-waves than the other three groups, but this difference disappeared at week 8.[64]

Histologic examination of the rats' eyes showed a single sparse layer of photoreceptor cells in unoperated eyes compared to four to six rows of photoreceptor cells in active implant eyes. However, in rats with an active implant in one eye and an inactive implant in the other eye, photoreceptor preservation occurred over both implants. The two eyes were indistinguishable in terms of morphologic preservation, but this did not result in functional preservation as measured

by ERG. Only the superior region of the retina near the implant experienced this morphologic preservation.[64]

The second of Chow's extension studies was designed to measure growth factor expression of Fgf2 and was composed of the same four arms as the first study, with the exception that inactive implants are referred to as "minimally electrically active implants." By week 4, the active implant group demonstrated significantly larger dark-adapted and light-adapted ERG b-waves than the control and minimally active implant groups. No group differences were noted in a-wave amplitudes.[64]

At day 9, Fgf2 expression was significantly elevated in the active implant eyes compared with all other eyes, and there appeared to be a dose-response relationship (i.e., higher to lower Fgf2 expression in the active, minimally active, sham, and unoperated groups). At 30 days after implantation, the active implant eyes still had significantly greater expression of Fgf2 than the other three treatment arms, but Fgf2 expression was slightly lower than at postoperative day 9. This finding suggests that subretinal electrical stimulation from an implant confers benefit over and above the presence of nonactive chip placement or the surgical procedure alone. No between-group differences were observed in Fgf1, Cntf, Igf, Gdnf, or Bdnf.[64]

Before his death, the RP patient in the cadaver study reported subjective improvements after ASR implantation, but these subjective impressions did not correlate with objective tests. Chow attributed this lack of correlation to insensitivity of the objective tests. Upon death, the man's eyes were enucleated within 10 minutes after death and examined. Both retinas appeared to be in late stages of photoreceptor degeneration, with massive reorganization and remodeling. However, in the area over and in close proximity to the implant, the retina maintained some inner nuclear layer cells and inner plexiform layer structure. This pattern was not observed in the man's unimplanted eye. Compared with other retinal regions, both eyes showed a thicker fibrous glial cell layer on the inner side of the retina and around the implant, indicating substantial remodeling.[64]

Rizzo et al. found that compared to preimplantation, all six patients in whom the Argus II was implanted for 12 months experienced an improvement in their visual field when tested with the Goldmann visual field test. The authors did not present visual field test results with the System in ON mode.

Key Question 4. Adverse Events of RPSs

Description of Included Studies

Of the 10 studies included for KQ2, 9 reported adverse events (the only exception was Chow et al. 2010 and Geruschat et al. 2013 reports on the extension study).[64,65] The reported adverse event data appear in Table C-25 of Appendix C.

Key Points

- Intraoperative adverse events occurred in just over half of studies reporting this outcome, with trauma to the optic nerve being the most serious.
- Postimplantation adverse events were common and typically mild, including inflammation, temporary intraocular pressure (IOP) increase, eye scratchiness, and eye-movement restrictions.

- Intraoperative explantation adverse events were reported in half of the studies reporting this outcome, the most serious being a central retinal defect caused by removal of loose tacks.
- Post-explantation adverse events were reported by half of the studies reporting this outcome, with the most serious events including a decrease in visual acuity and a retinal detachment.
- Serious adverse events were reported by just under half of the studies reporting this outcome and included IOP increase, hypotony, and presumed endophthalmitis.
- Device-related adverse events were reported by a third of studies reporting this outcome and included device failure and need for retacking.
- Adverse events at the long-term followup were reported by just over half of studies reporting this outcome and were varied.

Detailed Synthesis

Device implantation intraoperative adverse events were reported by five studies.[14,18,52,53,61,66-70] Two studies indicated no intraoperative events.[18,66-70] One study each reported subretinal bleeding with complete reabsorption by day 10 in one patient,[14] device malfunction associated with optic disc swelling due to trauma to the optic nerve in one patient,[52,53] and touching and pulling of the ciliary body in one patient.[61]

Five studies reported the occurrence of adverse events in the post-implantation period. Klauke et al. and other authors found a mild inflammatory response in two patients, a significant inflammatory response with a painless hypopyon without chemosis in one patient, and hypotony with a flat anterior chamber, inflammation, and epiretinal proliferation at the central tack in one patient.[66-70] All three patients in the study conducted by Ayton et al. experienced a subretinal hemorrhage, pain, and mild inflammation while one patient each experienced eye-movement limitations and a staphylococcus infection.[18] Both patients in the study conducted by Fujikado et al. also experienced eye-movement restriction.[22] Chow et al. reported that several patients experienced eye scratchiness, three patients had elevated IOP, and one patient each had aniseikonia (image in one eye differs in size and shape from the image seen by the other eye) and syneresis (floaters).[21] Rizzo et al. also found elevated IOP in one patient as well as a choroidal detachment in one patient.[61]

Intraoperative explantation adverse events were reported in four studies. Klauke et al. and other authors reported two patients with loose tacks requiring removal, which led to a central retinal defect in one of these patients;[66-70] Zrenner et al. reported one patient with a mild skin infection of the retroauricular cable exit;[14] and Fujikado et al.[22] and Rizzo et al.[61] found no intraoperative adverse events during explantation surgery.

Post-explantation adverse events were reported in four studies. Klauke et al. and other authors found mild epiretinal gliosis formation at the tack fixation site in four patients and a temporary decrease in visual acuity in one patient through the 6-month followup visit.[66-70] Stingl et al. reported a retinal detachment immediately after explantation, which was treated surgically and resolved with local retinal fibrotic changes in one patient.[52,53] Both Fujikado[22] and Chow[21] reported no post-explantation adverse events.

Five investigators categorized adverse events as serious or nonserious and did not tie those events to a specific followup time. Arevalo,[62,63] Zrenner,[14] and Rizzo[61] reported that no serious adverse events occurred throughout the study period. Stingl[52,53] reported IOP elevation to 46 mm Hg in one patient, which was treated without sequel. Ho et al. and other authors[15,27,54-60] reported

subconjunctival erosion and hypotony in four patients, conjunctival dehiscence and presumed endophthalmitis in three patients, and corneal opacity, rhegmatogenous retinal detachment, tractional and serous retinal detachment, retinal tear, uveitis, infective uveitis, and corneal melt in one patient each. Ho reports that most serious adverse events occurred within the first 6 months after implantation and those that occurred more than 1 year after implantation were "part of a cascade of events that had begun earlier."

Six investigators reported the incidence of device-related adverse events. Arevalo,[62,63] Ayton,[18] Chow,[21] and Rizzo[61] reported that no device-related events occurred throughout the study followup period. Stingl[52,53] reported that an unspecified number of patients experienced infraorbital cable-part breaks due to stress from eye movements and one patient each experienced a device technical failure, retinal perfusion overlying the device, and retinal edema leading to device failure. Ho et al. and other authors[15,27,54-60] reported that seven patients elected to have revision surgery, two patients required retacking, and one patient experienced fibrosis around the tack, but no device failures occurred. Through an average of 6.2 years of followup, 24 patients still had functioning devices.

The occurrence of adverse events over the course of long-term followup (>6 months) was reported by five investigators. Klauke et al. and other authors[66-70] reported nonprogressive gliosis in four patients, slightly reduced visual acuity (in one case in association with retinal tack removal) in two patients, conjunctivitis in one patient, and an inflammatory reaction due to corneal sutures in one patient. Arevalo[62,63] reported edema in two patients, and elevated IOP, pain, suture irritation, and conjunctival erosion in one patient each over the approximate 1.5-year followup period. Ho et al. and other authors reported a long list of nonserious adverse events through the 3-year followup, with most occurring within the first year after implantation.[15,27,54-60] The most common events included epiretinal membrane in 11 patients, conjunctival congestion in 10 patients, ocular pain in 9 patients, hypotony in 7 patients, suture irritation and choroidal detachment in 6 patients, and uveitis and macular edema in 5 patients. Additionally, both patients who received the Argus II implant and subsequently had an magnetic resonance imaging (MRI) scan experienced local moderate paramagnetic artifacts approximately 50×50 mm that precluded clear visualization of the intraorbital space near the implant. Chow[21] and Rizzo[61] found no adverse events at their studies' final followup visit, which occurred 6–18 months after implantation for Chow and at 12 months for Rizzo.

Key Question 5A. Off-label use of RPSs

Description of Included Studies

We identified a single ongoing clinical trial of Argus II in patients with severe dry AMD that is due to be completed in June 2019. We also identified two relevant press releases.

Key Points

- One clinical trial of Argus II in patients with severe dry AMD is ongoing.

Detailed Synthesis

For the Argus II, the FDA indication is "for use in patients with severe to profound retinitis pigmentosa who meet the following criteria:

- Adults, age 25 years or older.

- Bare light or no light perception in both eyes. (If the patient has no residual light perception, then evidence of intact inner layer retina function must be confirmed.)
- Previous history of useful form vision.
- Aphakic or pseudophakic. (If the patient is phakic prior to implant, the natural lens will be removed during the implant procedure.)
- Patients who are willing and able to receive the recommended post-implant clinical followup, device fitting, and visual rehabilitation."

In Europe, the device is approved for use in patients with slightly better, hand motion vision,[79] and can be used in patients 18 years of age or older, based on patient recruitment at sites outside the United States.

Numerous reviews have suggested that patients with advanced AMD may be candidates for retinal prostheses, and this would be an off-label use, according to FDA criteria. No completed studies in AMD have been identified, but one clinical trial is under way. See Table C-26.

One news release from November 2015 indicated that both Pixium Vision and Second Sight are developing next-generation products to target AMD.[80] A 2015 press release of the American Society of Retina Specialists quotes one Argus II investigator suggesting that the company may explore the use of Argus II or another similar RPS in patients with a retinal detachment, whose retina has been reattached but whose vision has not been restored to an acceptable level.[79]

Key Question 5B. Other Uses of RPSs

We did not identify any information to address the use of RPSs for nonvisual uses. As noted above, one trial is ongoing, testing the Argus II device in patients with diagnosed dry AMD (NCT02227498).

Discussion

Key Findings and Strength of Evidence

The retinal prosthesis system (RPS) studies assessed in this review reported 73 different outcomes, mostly dealing with visual acuity (59 percent) or laboratory function (27 percent). Day-to-day visual function and quality of life were rarely measured. Little consensus exists among authors of RPS studies about which specific measures are important.

There is some evidence for the validity and/or reliability of the Early Treatment of Diabetic Retinopathy Study (ETDRS), Grating Acuity Test (GAT), Chow Color Test (CCT), and Functional Low-Vision Observer Rated Assessment (FLORA). No included evidence on patients with very low vision addressed the validity or reliability of other outcomes reported in the RPS studies.

Future RPS studies should consider measuring the following outcomes because some evidence shows that they are valid and/or reliable measures: full-field flash test, Grating Contrast Sensitivity (GCS), the patient and clinician version of the Functional Assessment of Self-Reliance on Tasks (FAST) instrument, the Very Low Vision Instrumental Activities of Daily Living (IADL-VLV), the Modified National Eye Institute Visual Function Questionnaire 25-item (NEI-VFQ-25) plus supplement, and the Modified Impact of Vision Impairment (IVI).

During our interviews with KIs, in particular patient/advocate KIs, we learned that patients vary in what they expect from a treatment like RPS implantation. Some patients hope to have their sight restored to "normal" vision. Other patients would be satisfied with more modest gains, such as the ability to color coordinate their clothing, use a color-contrast cutting board, or, for those patients with comorbid insulin-dependent diabetes, give themselves insulin injections. Retinal surgeons performing RPS implantation need to accurately present the full range of likely visual acuity gains and the possibility that any individual patient may not benefit from an implant.

When choosing outcomes to include in future RPS studies, investigators should routinely measure QOL and ADLs in addition to traditional visual acuity measures, as these measures are interrelated. Small gains in any vision measure (acuity, visual field, contrast sensitivity, color vision) has the potential to bring about clinically meaningful changes in QOL and ADLs from the patient's perspective.

Although some patients clearly experienced improved visual acuity, visual field, and visual function, the percentages varied greatly among studies of Moderate to High risk of bias. Thus, evidence is insufficient to estimate the proportion of patients who will benefit from an RPS.

There is some suggestion, based on both animal and human studies, that RPSs may have a neuroprotective effect that causes at least a temporary increase in vision in areas far away from the implantation site.

Intraoperative adverse events were reported in about half of all included studies, the most serious of which included injury to the optic nerve and central retinal defect. Postimplantation adverse events were common and typically mild, including inflammation, temporary intraocular pressure increase, eye scratchiness, and eye-movement restrictions. Serious adverse events were reported by just under half of the studies reporting this outcome and included intraocular pressure increase, hypotony, and presumed endophthalmitis.

Findings in Relationship to What is Already Known

To assess what is already known about the effectiveness and safety of retinal prostheses for retinitis pigmentosa (RP), we searched for pertinent systematic reviews and cost-effectiveness analyses. We identified one systematic review[81] and one cost-effectiveness analysis.[82] The cost-effectiveness analysis[82] did not offer an independent analysis of effectiveness or safety, since authors simply used the data from the Argus II study by Ho et al. and by other authors.[15,27,54-60] The systematic review was conducted by the National Institute for Health and Care Excellence (NICE) in the United Kingdom;[81] the last search date was December 31, 2014. The review included seven publications, and authors acknowledged that some of the publications may have had overlapping patient populations (they did not attempt to identify a set of unique studies). Regarding efficacy, the authors made no overarching statements about efficacy, but rather made five efficacy statements:

- In a case series of 30 patients implanted with an epiretinal prosthesis, improvements in visual acuity were reported in 23 percent (7/30 of patients at follow-up of up to 2.7 years. Visual acuity improved from worse than 2.9 logarithm of the minimum angle of resolution (logMAR) to between 2.9 and 1.6 logMAR (p value not reported).[81]
- In the case series of 30 patients, patients were asked to locate a white square that randomly appeared on a black liquid crystal display (LCD) touchscreen. Significantly better square localisation test results were reported in 96 percent (27/28) of patients when their prosthesis systems were switched on. No further details were provided.[81]
- In the case series of 30 patients, patients were asked to indicate the path of a white bar that swept across a black LCD touchscreen. Significantly better direction of motion test results were observed in 57 percent (16/28) of patients when their prosthesis systems were switched on. No further details were provided.[81]
- In the case series of 30 patients, patients were asked to stand in the center of a room, or offset left of center by 3 feet, or offset right of center by 3 feet. They were asked to find a rectangular "door" 20 feet away and to place their hand on it. The mean success rate was 60 percent when the prostheses were switched on compared against 5 percent when the prostheses were switched off, at 24‑month followup.[81]
- In a case series of 6 patients, the mean percentage of successful grasps of a white cube placed on a black surface was 69 percent when prostheses were switched on compared against 0 percent when prostheses were switched off, at 3‑year follow‑up. There was no significant difference between the proportion of successful grasps when patients' eyes were "patched" (both eyes taped closed) or "unpatched."[81]

All five statements were about the 30-patient Argus II study by Ho et al., also reported by other authors[15,27,54-60] (the 6-patient case series was a subset). The above statements merely reiterate the data, with no general synthesis of multiple studies. Similarly, regarding safety, the NICE review[81] simply reiterated data from the studies. Our review includes all the studies included by the NICE review, and several more. In the absence of other evidence syntheses,

given the recent introduction of this technology, we do not comment further on how our findings compare to what is already known.

Applicability

The patients enrolled in the 10 included RPS publications had RP, choroideremia, rod-cone dystrophy, or Bardet-Beidl syndrome and very low vision (counting fingers to no light perception) and are therefore representative of patients who will receive RPS devices in the future. Because there are no other treatments for patients with late-stage disease, the comparators used in these studies (pre- vs. post-implantation, system ON vs. OFF) were appropriate. One study specified that patients continued to use guide dogs throughout the study and typically underwent cataract removal in conjunction with the implantation procedure.

The maximum duration of study followup was 7 years. In the Argus II study, 24 of 30 patients still had functioning devices at a mean of 6.2 years followup. Because patients as young as 25 years of age may receive this device, longer-term followup is needed. One single patient cadaver study suggested that the ASR device had a functional life expectancy of about 20 years.

Outcomes reported in these studies were varied, making cross-study comparisons difficult. Additionally, outcomes were often not measured with valid and/or reliable instruments.

Only a limited number of sites are currently permitted to perform Argus II surgery, but that number will increase over time. Site personnel receive standardized training, so there is no reason to believe that future patients at hospitals not included in the Argus II feasibility studies would have poorer outcomes than the original multisite trial.

Implications for Clinical and Policy Decisionmaking

Due to inconsistencies in the evidence, this report makes no conclusions about the likelihood of patient benefit from RPS. Clearly, however, some patients do benefit. The magnitude of that benefit is unknown because of a paucity of evidence on quality of life and day-to-day function. However, for these patients, no other intervention exists to address their vision problems, so even small gains may be considered important for clinical and policy decisionmaking.

Limitations of the Systematic Review Process

The first set of challenges we faced involved literature searching. Even the best search strategies may fail to identify certain records; however, the chance of missing relevant studies is greatly reduced when searches are conducted, as they were for this report, across multiple resources using a combination of controlled vocabulary and keywords. Also, our information specialists searched the Web sites of selected medical association meetings for abstracts and presentation on retinal prosthetic devices.

Key Question 1C presented a particular search challenge, in that the scope of this question was extremely broad. To focus the search, the search strategies for this question (see Appendix A) included some additional limiting options, such as searching for controlled terms that had been indexed as a major focus of the article, and using additional terminology to identify studies that reported reliability, reproducibility, validity, and responsiveness. An additional bibliographic database, PsycINFO, was also introduced to ensure that relevant studies published in the psychological literature were captured.

Limitations of the Evidence Base

Two key limitations of the evidence base concern heterogeneity of interventions and comparators. First, the 10 studies used six different types of RPSs, and they are in different phases of development and testing. This means that the tested systems may differ in important ways from future versions. We excluded any systems that are known to be obsolete, in an effort to focus on our efforts on current systems. The only RPS that is cleared for marketing in the United States is the Argus II; therefore, this device's outcomes are likely more relevant to U.S. decisionmakers. Second, different studies used different comparators. Some compared patients' pre-implant performance to their post-implant performance. Others compared post-implant ON performance to post-implant OFF performance. Still others compared an implanted eye to an unimplanted eye (presuming that the patients' two eyes had similar acuity and function before implant, which is often not the case). And still others compared post-implant ON performance to a predefined level of chance performance. The variety of comparators clouded whatever true RPS benefits exist.

Another set of problems concerned the outcomes. We noted large variability in the types of outcomes used by authors in an effort to measure the impact of RPS. For visual acuity alone, 43 different outcomes were found in just 10 studies. Part of the reason for this is that visual acuity is a multifaceted concept. Even for a given acuity test, however, authors often reported data in different ways. The most common method was to report the proportion of patients who improved as compared to pre-implantation. Another method of reporting was to compare the proportion of patients who passed a test before versus after implantation (which differs subtly from the proportion improved, since some patients could pass a test both before and after, and yet still have improved). Other studies reported mean results of tests such as logarithm of the minimum angle of resolution (logMAR), the number of seconds to identify letters on a screen, or the total number of letters identified correctly. Furthermore, only four of the reported tests have been tested for psychometric properties (see Key Question 1B). Other tests are available (see Key Question 1C) that have been specifically developed for people with very low vision, and future authors of RPS studies should consider them.

A fourth limitation was the small size of the typical study of RPS. The median study enrollment was six patients. Furthermore, some enrolled patients did not receive all of the post-implantation tests, so the actual number of patients per study with data on certain outcomes was sometimes only one or two. These low counts are reflected in the wide confidence intervals around proportion estimates in figures for Key Question 2, as well as our ratings of imprecision during strength-of-evidence assessment. Granted, RPS is rare, and large studies are impractical. However, large imprecision results in little confidence in any estimate of the proportion of patients who would improve after RPS implantation.

Evidence Gaps

We used Evidence-based Practice Center guidance by Robinson et al.[83] to delineate reasons for the evidence gaps: A. Insufficient or imprecise information; B. Biased information; C. Inconsistency or unknown consistency; D. Not the right information.

The first identified gap is the paucity of direct information about how RPS affects quality of life. Only one of the 10 included RPS studies reported data on a quality-of-life instrument (the NEI-VFQ-25). Authors reported no statistically significant change in quality of life occurred during the 2-year study period. This does not mean there was no change, because the study was

too small (only 6 patients enrolled) to rule out the possibility of a difference. We recognize that the other reported outcomes (visual acuity, laboratory-based measures of function, day-to-day function) may be surrogates for quality of life (on the premise that improved acuity will translate into improved quality of life). However, these outcomes are less patient-oriented than quality of life itself. The reason for this gap is A: Insufficient or imprecise information.

The second identified gap is the inability to estimate the proportion of patients who improve after RPS implantation. Because studies used different devices, different comparators, and different outcomes (see previous section), there can be no single estimate of the proportion, because all of these aspects will likely affect improvement rates. Even controlling for type of RPS, there was too much outcome heterogeneity to permit an estimate. The reason for this gap is C: Inconsistency.

A third gap involved psychometric testing of outcome measures in patients with very low vision (Key Questions 1A and 1B). The studies we found used relatively advanced methods for testing psychometric properties (i.e., Rasch-based analysis, and separation of item difficulty from person ability). Several of these studies had devised new instruments specifically for people with very low vision. The 10 included RPS studies, however, generally did not use these tests (an exception was the Chow studies of the Artificial Silicon Retina,[21,64,65] which also provided psychometric properties of certain tests). The reason for this gap is D: Not the right information. We encourage greater use of tested instruments in future studies of RPS. With greater consistency of outcome measures, future evidence reviews might be able to estimate the likelihood of improvement after RPS implantation.

A fourth gap involves Key Question 5 (off-label uses and other uses of RPS), for which we found one ongoing trial of the Argus II device in patients diagnosed with dry age-related macular degeneration (AMD; NCT02227498). We summarized narrative reviews, and mention a few possible alternate uses. The reason for this gap is A: Insufficient or imprecise information.

Conclusion

Future studies of RPS devices should make an effort to report valid and reliable measures of important outcomes, especially day-to-day function, and quality of life.

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Abbreviations and Acronyms

AAO:	American Academy of Ophthalmology
ADL:	activities of daily living
ADLMS:	activities of daily living mobility and safety
AE:	adverse event
AFC:	alternative forced choice
AHRQ:	Agency for Healthcare Research and Quality
AMD:	age-related macular degeneration
ANOVA:	analysis of variance
AREDS:	Age-Related Eye Disease Study
ARVO:	Association for Research in Vision and Ophthalmology
ASR:	Artificial Silicon Retina
BaLM:	Basic Assessment of Light and Motion (BaLM) test
CCT:	Chow Color Test
CF:	counting fingers
CINAHL:	Cumulative Index to Nursing and Allied Health
cm:	centimeter
CMS:	U.S. Centers for Medicare and Medicaid
CNV:	choroidal neovascularization
COI:	conflict of interest
COSMIN:	COnsensus-based Standards for the selection of health Measurement Instruments
CoV:	coefficient of variation
$CR_{.95}$:	coefficient of repeatability
dB:	decibel
EPC:	Evidence-based Practice Center
ERG:	electroretinographic
ETDRS:	Early Treatment of Diabetic Retinopathy Study test
EWB:	emotional well-being
FAST:	Functional Assessment of Self-Reliance on Tasks
FDA:	U.S. Food and Drug Administration
FLORA:	Functional Low-Vision Observer Rated Assessment
FrACT:	Freiburg Acuity and Contrast Test
GA:	geographic atrophy
GAT:	Grating Acuity Test
GCS:	Grading Contrast Sensitivity test
HM:	hand motion
HRQoL:	health-related quality of life
IADL:	instrumental activities of daily living
IADL-VLV:	very low vision instrumental activities of daily living
IOP:	intraocular pressure
IVI:	Modified Impact of Vision Impairment
KI:	Key Informant
KQ:	Key Question
LCD:	liquid crystal display
LED:	light-emitting diode
logMAR:	logarithm of the minimum angle of resolution
LP:	light perception
mm Hg:	millimeters of mercury
MRI:	magnetic resonance imaging
NA:	not applicable
NEI-VFQ-25:	National Eye Institute Visual Function Questionnaire 25 item
NICE:	National Institute for Health and Care Excellence
NR:	not reported
OD:	*oculus dextrus*; right eye
OS:	*oculus sinister*; left eye
OUReP:	Okayama University-Type Retinal Prosthesis
PICOTS:	population, intervention, comparators, outcomes, timing, and setting
QOL:	quality of life
RCS:	Royal College of Surgeons
Rng:	range
RP:	retinitis pigmentosa
RPE:	retinal pigment epithelium
RPS:	retinal prosthesis system
SAE:	serious adverse event
SD:	standard deviation
STS:	Suprachoroidal Transretinal Stimulation
UK:	United Kingdom
VA:	Veterans Health Administration
VEGF:	vascular endothelial growth factor
VF:	visual field